(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2014 (20.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/028669 A1

(51) International Patent Classification:

A61K 31/10 (2006.01)	*C07C 317/28* (2006.01)
A61P 3/10 (2006.01)	*C07C 317/30* (2006.01)
C07D 213/75 (2006.01)	*C07D 407/04* (2006.01)
C07D 309/08 (2006.01)	*C07D 239/47* (2006.01)
C07D 405/04 (2006.01)	*C07D 413/04* (2006.01)
C07D 405/10 (2006.01)	*C07D 273/01* (2006.01)

(21) International Application Number:
PCT/US2013/055017

(22) International Filing Date:
14 August 2013 (14.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/683,651	15 August 2012 (15.08.2012)	US
61/786,278	14 March 2013 (14.03.2013)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/028669 A1

(54) Title: NOVEL COMPOUNDS FOR MODULATION OF ROR-GAMMA ACTIVITY

(57) Abstract: The present invention relates to aryl sulfones and related compounds that are modulators of ROR-gamma receptors. The invention also provides pharmaceutical compositions comprising these modulators, and methods of modulating ROR-gamma receptors using them. Also provided are methods of using aryl sulfones and related compounds as modulators of ROR-gamma to treat ROR-gamma mediated diseases.

NOVEL COMPOUNDS FOR MODULATION OF ROR-gamma ACTIVITY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application Serial Nos. 61/683,651, filed August 15, 2012 and 61/786,278, filed March 14, 2013, the disclosures of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to aryl sulfones and related compounds that are modulators of ROR-gamma activity. The invention also provides pharmaceutical compositions comprising these modulators. Also provided are methods of using these modulators to treat ROR-gamma mediated diseases.

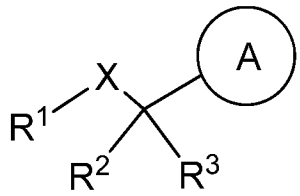
BACKGROUND OF THE INVENTION

[0003] Dysregulation of the immune system is a common cause of human disease. Autoimmune diseases occur when the immune system attacks and destroys healthy body tissue. Other inflammatory diseases, such as asthma, do not necessarily result from a direct attack on healthy tissue but rather from improper or uncontrolled immune responses. Agents that modulate the development and function of cells of the immune system can be useful as therapies for such diseases.

[0004] One method of achieving such modulation is by targeting the function of nuclear receptors expressed in the immune system. Nuclear receptors are a superfamily of ligand-regulated DNA-binding transcription factors that are expressed by many cell types and control a broad spectrum of physiological processes. Drugs that target nuclear receptors are used in the treatment of numerous human diseases. Pharmaceutical nuclear receptor agonists or antagonists, such as tamoxifen for oestrogen receptors (targeted in breast cancer), thiazolidinediones for peroxisome proliferator-activated receptor-γ (PPARγ) (targeted in type II diabetes), or dexamethasone for the glucocorticoid receptor (targeted in inflammatory diseases), are among the most commonly used drugs. The nuclear receptor, RAR-related orphan receptor C (RORC, ROR-gamma, ROR-gamma-t, and RORγ), is expressed in cells of the immune system and plays an important role in immune system function. Disclosed herein are aryl sulfones and related compounds that are useful as modulators of ROR-gamma activity.

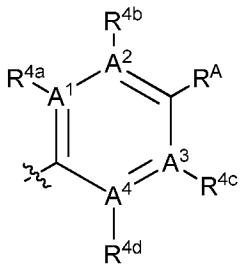
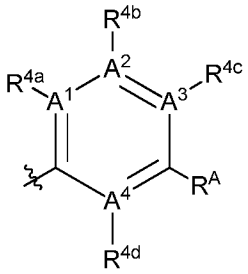
SUMMARY OF THE INVENTION

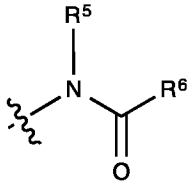
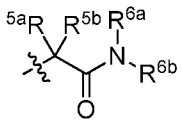
[0005] In one aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

A is  , or  ;

R^A is  ; or  ;

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

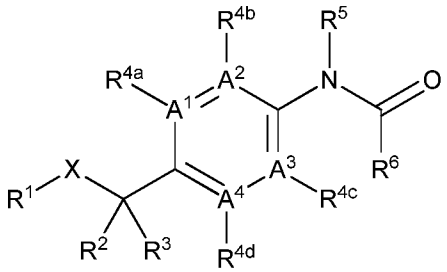
R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

R^{5a} and R^{5b} are each independently H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, R^{6a} and R^{6b} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or R^{6a} and R^{6b} together form an optionally substituted heterocycloalkyl ring; or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0006] In another aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of Formula Ia:



Formula Ia

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

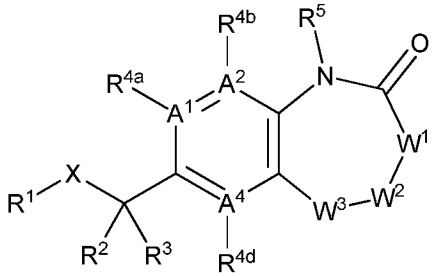
R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0007] In some embodiments of Formula I, and Ia, R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring, as shown in Formula Ia^1:



Formula Ia^1

or a pharmaceutically acceptable salt thereof,

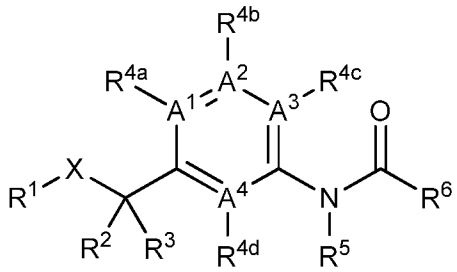
wherein:

W^1 is $CR^{7a}R^{7b}$, NR^{7c}, or O;

W^2 and W^3 are each independently $CR^{7a}R^{7b}$, NR^{7c}, O, or a bond; and

R^{7a}, R^{7b}, and R^{7c} are each independently H or C_{1-4} alkyl.

[0008] In another aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of Formula Ib:



Formula Ib

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;
R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;
R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;
R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or
R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0009] The compounds of Formula I, Formula Ia, Formula Ia^1, and Formula Ib can include one or more of the following embodiments.

[0010] In one embodiment, R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, carboxyl, and acetyl.

[0011] In another embodiment, R^2 and R^3 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted OC_{1-6} alkyl, CN, OH.

[0012] In still another embodiment, R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted carbocycle, or optionally substituted heterocycle.

[0013] In yet another embodiment, R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted carbocycle, or optionally substituted heterocycle; and R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, carboxyl, and acetyl.

[0014] In a further embodiment, R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally

substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted carbocycle, or optionally substituted heterocycle; and R^2 and R^3 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted OC_{1-6} alkyl, CN, OH.

[0015] In several embodiments, R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring.

[0016] In another aspect, the invention includes a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or adjuvant.

[0017] In another aspect, the invention includes a method of modulating the activity of an ROR-gamma receptor with a modulator of ROR-gamma, comprising contacting the receptor with a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0018] In one embodiment of this aspect, the compound of Formula I modulates the activity of an ROR-gamma receptor *in vitro*. In another embodiment, the compound of Formula I modulates the activity of an ROR-gamma receptor *in vivo*. In one embodiment, the compound of Formula I is a modulator of the ROR-gamma receptor.

[0019] In yet another aspect, the invention includes a method of treating or reducing the severity of an ROR-gamma receptor mediated disease in a patient comprising administering a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0020] In one embodiment of this aspect, an ROR-gamma receptor mediated disease can include an automimmune disease. In some embodiments, an autoimmune disease is selected from the group consisting of Ankylosing spondylitis, Asthma, Behcet's disease, Chronic obstructive pulmonary disease, Crohn's disease, Diabetes Mellitus Type 1, Multiple Sclerosis, Neuromyelitis optica, Polymyalgia Rheumatica, Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, Scleroderma, Sjögren's syndrome, Systemic Lupus Erythematosus, Systemic sclerosis, Transplant rejection, Inflammatory Bowel Disease, Ulcerative Colitis and Uveitis.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0021] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausolito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0022] As used herein the term "aliphatic' encompasses the terms alkyl, alkenyl, alkynyl. Unless otherwise stated, aliphatic can include both substituted alkyl, alkenyl, and alkynyl and unsubstituted alkyl, alkenyl, and alkynyl.

[0023] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6, 1-4, or 1, 2, 3, 4, 5, 6, 7, or 8) carbon atoms. As used herein, the terminology C_{1-n} alkyl refers to an alkyl group containing 1-n carbon atoms. For example, C_{1-5} alkyl refers to an alkyl group containing 1, 2, 3, 4, or 5 carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl.

[0024] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl, and 2-hexenyl.

[0025] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one triple bond. Like an alkyl group, an alkynyl group can be straight or branched.

[0026] As used herein, an "amino" group refers to $-NR^XR^Y$ wherein each of R^X and R^Y is independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, heteroaryl, or carbonyl each of which are defined herein. Examples of amino groups include alkylcarbonylamino, alkylsulfonylamino, alkoxycarbonylamino, (azacycloalkylcarbonyl)amino, heteroaralkylcarbonylamino, heteroarylcarbonylamino, carbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino,

(cycloalkyl)alkylcarbonylamino, cycloalkylcarbonylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above. A nonexhaustive list of possible R^X and R^Y includes sulfonylamino, alkylamino, carbonylamino, carboxy, oxo, hydroxyl, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, heterocycloalkylalkylcarbonyl, heteroarylcarbonyl, or heteroaralkylcarbonyl.

[0027] As used herein, a "carbonyl" group, when used alone or as part of another structure refers to $-(CO)R^X$, where R^X is defined above. When the term "carbonyl" is not the terminal group (e.g., arylaminoalkylcarbonyl) it is represented by $-C(O)R^X$. Without limitation, carbonyl groups can include optionally substituted aminocarbonyl, alkoxyalkoxycarbonyl, alkylaminocarbonyl, arylcarbonyl (e.g., haloarylcarbonyl), heterocycloalkylcarbonyl, heterocycloalkenylcarbonyl, arylaminocarbonyl (e.g., haloarylaminocarbonyl), cyanoalkylarylcarbonyl, heterocycloalkoxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, heterobicycloarylcarbonyl, alkylheteroarylaminocarbonyl, alkoxyarylcarbonyl (e.g., haloalkoxyarylcarbonyl), (alkylheterocyclo)alkenylcarbonyl, heteroarylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl (e.g., haloalkoxycarbonyl), alkylarylcarbonyl, cycloalkylcarbonyl, alkylheteroarylcarbonyl, arylsulfonylcarbonyl, aminocarbonyl, sulfonylcarbonyl, alkylcarbonyl, alkylsulfonylcarbonyl, alkylcarbonyl, arylaminocarbonyl, or the like. A nonexhaustive list of possible R^X and R^Y includes sulfonylaminocarbonyl, alkylcarbonyl, carbonylamino, carboxy, oxo, hydroxyl, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, heterocycloalkylalkylcarbonyl, heteroarylcarbonyl, or heteroaralkylcarbonyl.

[0028] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to an aromatic monocyclic ring ((e.g., phenyl); an aromatic C_8-C_{10} bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); an aromatic C_{10}-C_{14} tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, anthracenyl, or tetrahydroanthracenyl); or a C_8-C_{14} benzofused group having 2-3 carbocyclic rings in which one or more of the rings are aromatic. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties.

[0029] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group)

that is substituted with an aryl group. Both "alkyl" and "aryl" are defined herein. An example of an aralkyl group is benzyl.

[0030] A "heteroaralkyl" group refers to an alkyl group that is substituted with a heteroaryl. Both "alkyl" and "heteroaryl" are defined herein.

[0031] The term "cycloaliphatic" means a saturated or partially unsaturated monocyclic, bicyclic, or tricyclic hydrocarbon ring that has a single point of attachment to the rest of the molecule. Cycloaliphatic rings are 3-8 membered monocyclic rings (e.g., 3-6 membered rings). Cycloaliphatic rings also include 8-12 membered bicyclic hydrocarbon rings, (e.g., 10 membered bicyclic hydrocarbon rings). A cycloaliphatic group encompasses a "cycloalkyl" group and a "cycloalkenyl" group.

[0032] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono-, bi-, tri-, or multicyclic (fused or bridged) ring of 3-10 (e.g., 4-6, 5-10, 3, 4, 5, 6, 7, 8, 9, or 10) carbon atoms. Without limitation, examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or the like. Without limitation, examples of bicyclic cycloalkyl groups include octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, bicycle[2.2.1]heptanyl, bicycle[3.1.1]heptanyl, or the like. Without limitation, multicyclic groups include adamantyl, cubyl, norbornyl, or the like.

[0033] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, and bicyclo[3.3.1]nonenyl.

[0034] The terms "spiro," "spirocycle," or "spirocyclic," or "spirocyclyl" as used herein, refer to two rings joined by a single carbon atom common to both, wherein the spirocyclyl ring system has 3-14 (e.g., 4-6, 5-10, 6-12, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14) carbon atoms. Examples of spirocyclyl groups include spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[2.6]nonanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[3.6]decanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, spiro[4.6]undecanyl, spiro[5.5]undecanyl, spiro[5.6]dodecanyl, or spiro[6.6.]tridecanyl.

[0035] The terms "carbocycle," "carbocyclic" or "carbocyclyl" as used herein indicates a fully saturated, partially saturated, or unsaturated C_{3-10} monocyclic or bicyclic ring having only carbon ring atoms. Bicyclic carbocycles may be fused or spirocyclic ring systems. C_{3-10}

carbocyclic groups include fully saturated cycloalkyl rings (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl rings); partially saturated carbocyclic groups (e.g., cyclopropene, cyclobutene, cyclopentene and cyclohexene rings); bicyclic moieties (e.g., indene, 2,3-dihydro-indene, and 1,2,3,4-tetrahydronaphthalene groups); bridged moieties (e.g., bicyclo[3.1.0]hexane, bicyclo[3.2.1]octane, and bicyclo[3.1 .1]heptane groups); and spirocyclic carbocycles (e.g., spiro[2.3]hexane, spiro[2.4]hexane, spiro[3.3]heptane, spiro[3.4]octane, spiro[2.5]octane, spiro[4.5]decane and spiro[5.5]hendecane). Unsaturated carbocyclic moieties include phenyl and naphthyl groups.

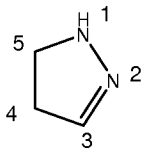
[0036] It will be understood that the terms listed above for heterocycles includes each possible atomic orientation for the groups listed. For instance, the term oxadiazole includes 1,2,3-oxadiazole, 1,3,4-oxadiazole and 1,2,4-oxadiazole; the term thiadiazole includes 1,2,3-thiadiazole, 1,3,4-thiadiazole and 1,2,4-thiadiazole.

[0037] The terms "heterocycle" or "heterocyclic," or "heterocyclyl" as used herein indicates a fully saturated, partially saturated, or unsaturated 3- to 12-membered monocyclic or bicyclic ring having from 1 to 5 ring heteroatoms selected from O, S or N. The bicyclic heterocycles may be fused or spirocyclic ring systems. Monocyclic or bicyclic heterocycles, alone, and together with fused or spirocyclic groups, include aziridines, oxirane, azetidine, azirine, thirene, oxetane, oxazetidine, tetrazole, oxadiazole, thiadiazole, triazole, isoxazole oxazole, oxathiazole, oxadiazolone, isothiazole, thiazole, imidazole, pyrazole, isopyrazole, diazine, oxazine, dioxazine, oxadiazine, thiadiazine, oxathiazole, triazine, thiazine, dithiazine, tetrazine, pentazine, pyrazolidine, pyrrole, pyrrolidine, furan, thiophene, isothiophene, tetrazine, triazine, morpholine, thiazine, piperazine, pyrazine, pyridazine, pyrimidine, piperidine, pyridine, pyran, thiopyran, azepine, diazepine, triazepine, azepane, 3-aza-bicylco[3.2.1]octane, 2-lo aza-bicylco[2.2.1]heptane, octahydrocyclopentapyrrole, aza-bicyclo-nonane, indole, indoline, isoindoline, indolizine, octahydro-isoindole, 2-azaspiro[4.5]decane, 6-azaspiro[2.5]octane, 7-azaspiro[3.5]nonane, 8-azaspiro[4.5]decane, 3-asaspiro[5.5]undecane, 1-oxa-7-azaspiro[4.4]nonane, 1-oxa-8-azaspiro[4.5]decane, purine, benzothiazole, benzoxazole, indazole, benzofuran, and isobenzofuran. Examples of spirocyclic heterocycles include oxaspiro[2.3]hexaneI 1-oxaspiro[3.4]octane, 1-oxaspiro[2.5]octaneI 2-oxaspiro[4.5]decane, 2,6-diazaspiro[3.2]heptane, azaspiro[2.5]octane, 6-aza-spiro[2.5]octane, 1,6-diazaspiro[2.5]octane, 7-aza-spiro[3.5]nonane, 3-aza-spiro[5.5]undecane, 8-azaspiro[4.5]decane, 1,3-diazaspiro[4.5]decane, 2,8-diazaspiro[5.5]hendecaneI 3,9- diazaspir0[5.5]hendecane, and 1-ox-6-azaspiro[2.5]octane. It will be understood that the terms listed above for heterocycles includes each possible atomic

orientation for the groups listed. For instance, the term oxadiazole includes 1,2,3-oxadiazole, 1,3,4-oxadiazole and 1,2,4-oxadiazole; the term thiadiazole.

[0038] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono or bicyclic (fused or bridged) (e.g., 4-6, 5-10, 3, 4, 5, 6, 7, 8, 9, or 10-membered mono or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydro-benzofuryl, octahydro-chromenyl, octahydro-thiochromenyl, octahydro-indolyl, octahydro-pyrindinyl, decahydro-quinolinyl, octahydro-benzo[*b*]thiopheneyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octanyl, 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl, tropane. A monocyclic heterocycloalkyl group may be fused with a phenyl moiety such as tetrahydroisoquinoline. Heterocycloalkyl ring structures can be optionally substituted at any chemically viable position on the ring or rings.

[0039] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicylic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Examples of heterocycloalkenyls include 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, or 2-pyrazolyl. Monocyclic heteroaliphatics are numbered according to standard chemical nomenclature. For instance:

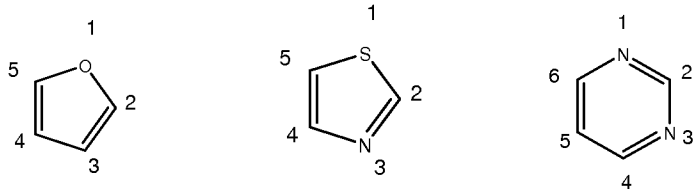


2-Pyrazoline.

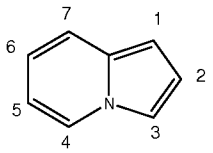
[0040] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring structure having 4 to 15 (e.g., 5-9, 6-13, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof), and wherein one or more rings of the bicyclic or tricyclic ring structure is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two C_{4-8} heterocyclic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidinyl, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl,

isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[*b*]furyl, benzo[*b*]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

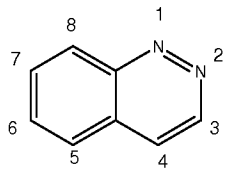
[0041] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature. For instance:



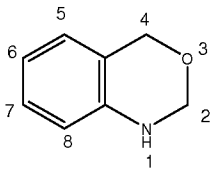
[0042] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolizyl, isoindolyl, indazolyl, benzimidazyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, indolizinyl, imidazopyridinyl, tetrahydrobenzoazepinyl, tetrahydrobenzooxazepinyl, benzo[1,4]oxazinyl, benzodihydro[1,4]oxazinyl, benzo[1,3]oxazinyl, benzodihydro[1,3]oxazinyl, fused pyrido[1,4]oxazinyl, fused pyrido[1,3]oxazinyl, fused pyrido[1,4]dihydrooxazinyl, fused pyrido[1,3]dihydrooxazinyl, fused pyrimido[1,4]oxazinyl, fused pyrimido[1,3]oxazinyl, fused pyrimido[1,4]dihydrooxazinyl, fused pyrimido[1,3]dihydrooxazinyl, fused pyrizo[1,4]oxazinyl, fused pyrizo[1,3]oxazinyl, fused pyrizo[1,4]dihydrooxazinyl or fused pyrizo[1,3]dihydrooxazinyl or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature. For instance:



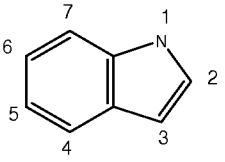
Indolizine



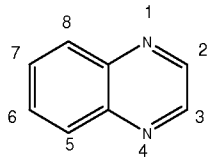
Cinnoline



3,1-Benzoxazine



Indolizine



Quinoxaline

[0043] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above.

[0044] As used herein, "cyclic moiety" includes cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, each of which has been defined previously.

[0045] As used herein, "cycloketonyl" refers to a cycloaliphatic moiety where at least one carbon atom of the ring forms a double bond to oxygen. Examples of cycloketonyl compounds include cyclobutonyl, cyclopentonyl, cyclohexonyl, and cycloheptonyl.

[0046] As used herein, an "acyl" group refers to a formyl group or alkyl-C(=O)- (also referred to as "alkylcarbonyl") where "alkyl" has been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0047] As used herein, a "carbamoyl" group refers to a group having the structure -O-CO-NR^xR^y or -NR^x-CO-O-R^z wherein R^x and R^y have been defined above and R^z can be alkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroaralkyl.

[0048] As used herein, a "carboxy" (or "carboxyl") and a "sulfo" group refer to –COOH or -$COOR^X$ and -SO_3H or -SO_3R^X, respectively.

[0049] As used herein, a "hydroxy" or "hydroxyl" group refers to –OH.

[0050] As used herein, an "alkoxy" or "alkoxyl" group refers to an alkyl-O- group where "alkyl" has been defined previously. Moreover an alkoxy group includes structures comprising two alkoxy groups on the same atom or adjacent atoms that form a ring together with the atom(s) to which they are bound.

[0051] As used herein, a "sulfoxy" group refers to -O-SO-R^X or –SO-O-R^X, where R^X has been defined above.

[0052] As used herein, a "mercapto" group refers to –SH.

[0053] As used herein, a "sulfonyl" group refers to $–S(O)_2-R^X$, wherein R^X has been defined above. Examples of sulfonyls include optionally substituted alkylsulfonyl, arylsulfonyl (e.g., haloarylsulfonyl), heteroarylsulfonyl (e.g., alkylheteroarylsulfonyl), or the like.

[0054] As used herein a "sulfinyl" group refers to $–S(O)-R^X$, wherein R^X has been defined above. Examples of sulfinyls include alkylsulfinyl.

[0055] As used herein a "sulfanyl" group refers to $–S-R^X$, wherein R^X has been defined above. Examples of sulfanyls include alkylsulfanyl.

[0056] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[0057] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen atoms on each carbon atom. For instance, the term haloalkyl includes the group $-CF_3$.

[0058] As used herein, a "sulfamoyl" group refers to the structure $-S(O)_2-NR^xR^y$ or $-NR^x-S(O)_2-R^z$ wherein R^x, R^y, and R^z have been defined above.

[0059] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^YR^Z$ wherein R^X, R^Y, and R^Z have been defined above.

[0060] As used herein, a "carbonylamino" group used alone or in connection with another group refers to an amido group such as $Rx-C(O)-NR^X-$. For instance an alkylcarbonylamino includes $alkyl-C(O)-NR^X-$, wherein R^x has been defined above.

[0061] As used herein, a "aminocarbonyl" group used alone or in connection with another group refers to an amido group such as $N(Rx)_2-C(O)-$.

[0062] As used herein, an "alkoxycarbonyl" used alone or in connection with another group refers to a carbonyl group such as alkyl-O-C(O)-.

[0063] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[0064] As used herein, an "aminoalkoxyalkyl" refers to an alkyl group such as $N(R^x)_2$-alkyl-O-alkyl-, wherein R^x and alkyl have been defined above.

[0065] As used herein, "alkoxyalkylaminoalkyl" refers to an alkyl group such as alkyl-O-alkyl-$N(R^x)_2$-alkyl-, wherein alkoxy, R^x and alkyl have been defined above.

[0066] As used herein, an "aminocarbonyl" refers to an amido group such as -NR^X-C(O)-, wherein R^x has been defined above.

[0067] As used herein, an "aminosulfonyl" refers to the structure -$N(R^X)_2$-$S(O)_2$-, wherein R^x has been defined above.

[0068] As used herein, an "oxo" refers to =O.

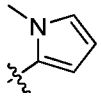
[0069] As used herein, an "aminoalkyl" refers to the structure $N(R^X)_2$-alkyl-.

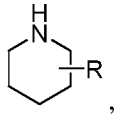
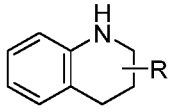
[0070] As used herein, a "cyanoalkyl" refers to the structure (CN)-alkyl-.

[0071] As used herein, an "alkylsulfonyl' group refers to the structure alkyl-$S(O)_2$-.

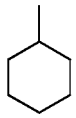
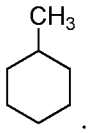
[0072] As used herein, a "sulfonylamino" group refers to the structure Rx-$S(O)_2$-$N(R^X)_2$-, wherein R^x has been defined above.

[0073] As used herein, a "urea" group refers to the structure -NR^X-CO-NR^YR^Z and a "thiourea" group refers to the structure -NR^X-CS-NR^YR^Z. R^X, R^Y, and R^Z have been defined above.

[0074] As used herein, pictured substituents drawn with a single, unattached wavy line drawn perpendicular to a bond of the substituent is meant to show the attachment point of the substituent. For example, the pyrrole substituent,  , is shown as attached to the main core structure by the ring nitrogen, while the pyrrole substituent,  , is shown as attached to the main core structure by the carbon atom adjacent to the ring nitrogen.

[0075] As used herein, pictured ring structures drawn with a substituent's bond overlayed on one of the ring bonds shows that the substituent can be at any substitutable atom of the entire ring structure, whether the ring structure is monocyclic or multicyclic. For example, the R substituent on the structure,  , can be substituted on any atom of the piperidine ring, and the R substituent on the structure,  , can be substituted on any atom of the benzene ring or piperidine ring.

[0076] As used herein, pictured structures having methyl substituents are drawn to show

those methyl substituents as an external bond. Specifically, the structure,  , is identical to the structure 

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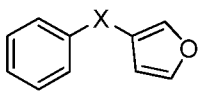
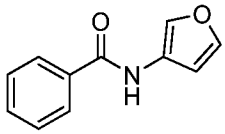
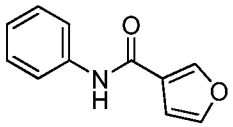
[0077] As depicted herein, divalent substituents, such as an amide, shown as –C(O)N(Rx)–, are meant to include the substituent in both directions. For example, the generic structure 

, wherein X is an unsubstituted amide can be 

or 

. Some examples of generic divalent substituents include, but are not limited to -CO-, -CS-, -$CONQ_2$-, -CO_2-, -OCO-, -NQ_2-, -NQ_2CO_2-, -O-, -NQ_2CONQ_2-, -$OCONQ_2$-, -NQ_2CO-, -S-, -SO-, -SO_2-, -SO_2NQ_2-, -NQ_2SO_2-, and -$NQ_2SO_2NQ_2$-.

[0078] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents can be bound to the same atom (carbon, nitrogen, oxygen) or two or more different atoms. A ring substituent, such as a heterocycloalkyl, may be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0079] Substituents can include, but are not limited to, alkyl, cycloalkyl, alkenyl, amino, carbonyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroaralkyl, acyl, carbamoyl, carboxy, hydroxyl, alkoxy, sulfoxy, mercapto, sulfonyl, sulfinyl, sulfanyl, halogen, haloaliphatic, haloalkoxy, cyano, sulfamoyl, sulfamide, carbonylamino, aminocarbonyl, alkoxycarbonyl, alkoxyalkyl, aminocarbonyl, aminosulfonyl,

oxo, aminoalkyl, aminoalkoxyalkyl, alkoxyalkylaminoalkyl, cyanoalkyl, alkylsulfonyl, and sulfonylamino.

[0080] In general, the term "unsubstituted" refers to a chemical moiety that includes no substituents.

[0081] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

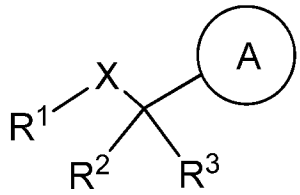
[0082] As used herein, an effective amount is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

[0083] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

Modulators of ROR-gamma activity

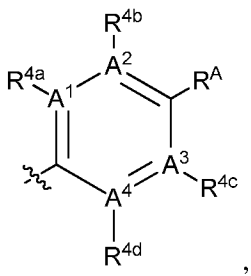
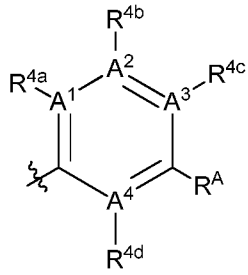
[0084] In one aspect, the invention provides aryl sulfones and related compounds that are

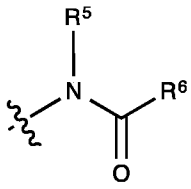
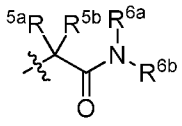
modulators of ROR-gamma activity, wherein the modulators are compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

A is  , or  ;

R^A is  ; or  ;

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

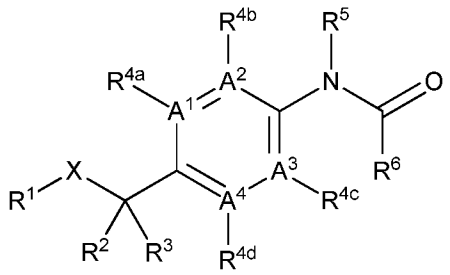
R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

R^{5a} and R^{5b} are each independently H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, R^{6a} and R^{6b} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or R^{6a} and R^{6b} together form an optionally substituted heterocycloalkyl ring; or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0085] In another aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of the Formula Ia:



Formula Ia

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

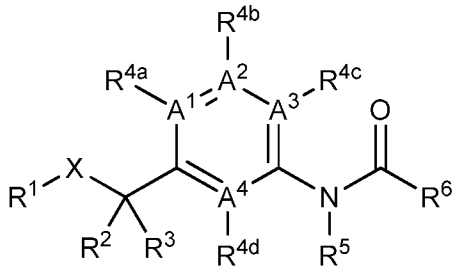
R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0086] In another aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of Formula Ib:



Formula Ib

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[0087] The compounds of Formula I and Formula Ia can include one or more of the following embodiments.

[0088] In some embodiments:

A^1, A^2, A^3, and A^4 are each C;

A^1, A^2, and A^4 are each C, and A^3 is N;

A^1, A^3, and A^4 are each C, and A^2 is N;

A^1 and A^4 are each C and A^2 and A^3 are each N; or

A^3 and A^4 are each C and A^1 and A^2 are each N.

[0089] In one embodiment:

A^1, A^2, and A^4 are each C; and

R^{4a}, R^{4b}, and R^{4d} are each H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

[0090] In a further embodiment, R^{4a}, R^{4b}, and R^{4d} are each independently C_{1-3} alkyl, OC_{1-3} alkyl, F, Cl, Br, or OH; wherein the C_{1-3} alkyl and OC_{1-3} alkyl are each optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some of these embodiments, R^{4a}, R^{4b}, and R^{4d} are each independently H, CH_3, C_2H_5, OCH_3, OC_2H_5, CH_3, CF_3, OCF_3, F, Cl, or OH. In other embodiments, R^{4a}, R^{4b}, and R^{4d} are each H.

[0091] In one embodiment:

A^1 and A^2 are each C, and A^4 is N;

R^{4a} and R^{4b} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and

R^{4d} is absent.

[0092] In a further embodiment, R^{4a} and R^{4b} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

[0093] In one embodiment:

A^1 and A^4 are each C, and A^2 is N;

R^{4a} and R^{4d} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and

R^{4b} is absent.

[0094] In a further embodiment, R^{4a} and R^{4d} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

[0095] In one embodiment:

A^2 and A^4 are each C, and A^1 is N;

R^{4b} and R^{4d} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and

R^{4a} is absent.

[0096] In a further embodiment, R^{4b} and R^{4d} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

[0097] In one embodiment:

A^1 and A^2 are each N, and A^4 is C;

R^{4a} and R^{4b} are each absent; and

R^{4d} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

[0098] In a further embodiment, R^{4d} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

[0099] In one embodiment:

A^1 and A^4 are each N, and A^2 is C;

R^{4a} and R^{4d} are each absent; and

R^{4b} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

[00100] In a further embodiment, R^{4b} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

[00101] In one embodiment:

A^2 and A^4 are each N, and A^1 is C;

R^{4b} and R^{4d} are each absent; and

R^{4a} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

[00102] In a further embodiment, R^{4a} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

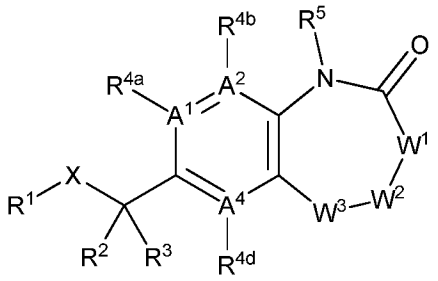
[00103] In one embodiment:

A^1, A^2, and A^4 are each N; and

R^{4a}, R^{4b}, and R^{4d} are each absent.

[00104] In some embodiments of Formula I and Ia, R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring as shown in Formula Ia^1.

[00105] In some embodiments of Formula I and Ia, R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring as shown in Formula Ia^1:



Formula Ia[1]

or a pharmaceutically acceptable salt thereof,

wherein:

W^1 is CR^{7a}, R^{7b}, NR^{7c}, or O;

W^2 and W^3 are each independently CR^{7a} R^{7b}, NR^{7c}, O, or a bond; and

R^{7a}, R^{7b}, and R^{7c} are each independently H or C_{1-4} alkyl.

[00106] In some of embodiments of Formula Ia[1]:

A^1, A^2, and A^4 are each C.

[00107] In some embodiments of the compounds of Formula Ia[1] include the following:

W^1 is $CR^{7a}R^{7b}$, and W^2 and W^3 are each $CR^{7a}R^{7b}$ or a bond;

W^1 is O, and W^2 and W^3 are each $CR^{7a}R^{7b}$ or a bond;

W^2 is O, and W^1 and W^3 are each $CR^{7a}R^{7b}$ or a bond;

W^3 is O, and W^1 and W^2 are each $CR^{7a}R^{7b}$ or a bond; or

R^{7a} and R^{7b} are each independently H or C_{1-3}alkyl.

[00108] In some embodiments of the compounds of Formula Ia[1] include the following:

W^1 and W^2 are each $CR^{7a}R^{7b}$;

W^3 is O; and

R^{7a} and R^{7b} are each independently H or CH_3.

[00109] For example, W^1 is $C(CH_3)(CH_3)$ and W^2 is CH_2.

[00110] The compounds of Formula I, Formula Ia, Formula Ib, and Formula Ia[1] can include one or more of the following embodiments.

[00111] In one embodiment, R^2 and R^3 together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[00112] In another embodiment, R^1 is optionally substituted carbocyclyl , and R^5 is an optionally substituted alkyl, or optionally substituted carbocyclyl.

[00113] In a further embodiment, one of R^{4a}, R^{4b}, and R^{4d} is H and the remaining are each

independently C_{1-3} alkyl, OC_{1-3} alkyl, F, Cl, Br, or OH; wherein the C_{1-3} alkyl and OC_{1-3} alkyl are each optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some of these embodiments, R^{4a}, R^{4b}, and R^{4d} are each independently H, CH_3, C_2H_5, OCH_3, OC_2H_5, CH_3, CF_3, OCF_3, F, Cl, or OH. In other embodiments, R^{4a}, R^{4b}, and R^{4d} are each H.

[00114] In still other embodiments, R^{4a}, R^{4b}, and R^{4d} are H, halogen, optionally substituted alkyl or absent.

[00115] In some embodiments, R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, OC_{1-4} alkyl, halogen, CN, OH, or absent.

[00116] In some exemplary embodiments:

R^{4a} is H, C_{1-3} alkyl, OC_{1-3} alkyl, or absent;
R^{4b} is H, C_{1-3} alkyl, OC_{1-3} alkyl, F, Cl, Br, haloalkyl, or absent;
R^{4c} is H, C_{1-3} alkyl, OC_{1-3} alkyl, or absent; and
R^{4d} is H, C_{1-3} alkyl, OC_{1-3} alkyl.

[00117] In other exemplary embodiments:

R^{4a} is H, C_{1-3} alkyl, or absent;
R^{4b} is H, C_{1-3} alkyl, Cl, CF_3, or absent;
R^{4c} is H, C_{1-3} alkyl, or absent; and
R^{4d} is H or C_{1-3} alkyl.

[00118] In some embodiments, R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, carboxyl, and acetyl. In some of these embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, or carboxyl.

[00119] In some embodiments, R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, oxo, amino, carboxyl, acetyl, alkyl-OH, haloalkyl,

and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and each n is independently 1 or 2.

[00120] In some embodiments, R^2 and R^3 together form cycloalkyl optionally substituted with aminoalkoxyalkyl, alkoxyalkylaminoalkyl or (C_{1-4} alkoxy)$_2$.

[00121] In some embodiments, R^2 and R^3 together form cycloalkyl optionally substituted with -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

[00122] In some embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl, each independently is optionally substituted with aminoalkoxyalkyl, alkoxyalkylamino alkyl or (C_{1-4} alkoxy)$_2$.

[00123] In some embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl, each independently is optionally substituted with -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

[00124] In some embodiments, R^2 and R^3 together form cyclopropyl optionally substituted with aminoalkoxyalkyl, alkoxyalkylamino alkyl or (C_{1-4} alkoxy)$_2$

[00125] In some embodiments, R^2 and R^3 together form cyclopropyl optionally substituted with -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

[00126] In some embodiments, R^2 and R^3 together form cyclopropyl optionally substituted with ethanol, propan-2-ol, methoxypropane, difluoroethane, 2-ethoxy-N,N-dimethylethanamine, 1-ethoxy-2-methoxyethane, N-ethyl-2-methoxyethanamine, or N-ethyl-2-methoxy-N-methylethanamine.

[00127] In some embodiments, R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl.

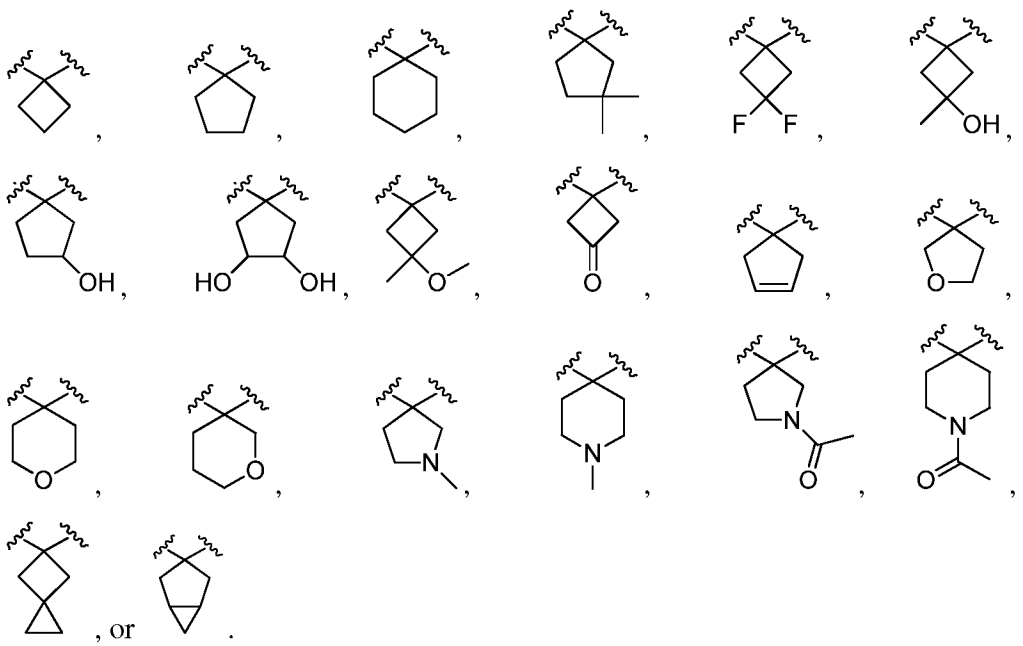
[00128] In several embodiments, R^2 and R^3 together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring. In some of these embodiments, X is SO_2. In some of these embodiments, R^1 is optionally substituted carbocycle. In some of these embodiments, R^5, and R^6 are each independently H, optionally substituted alkyl or optionally substituted carbocycle. In some of these embodiments, R^{4a},

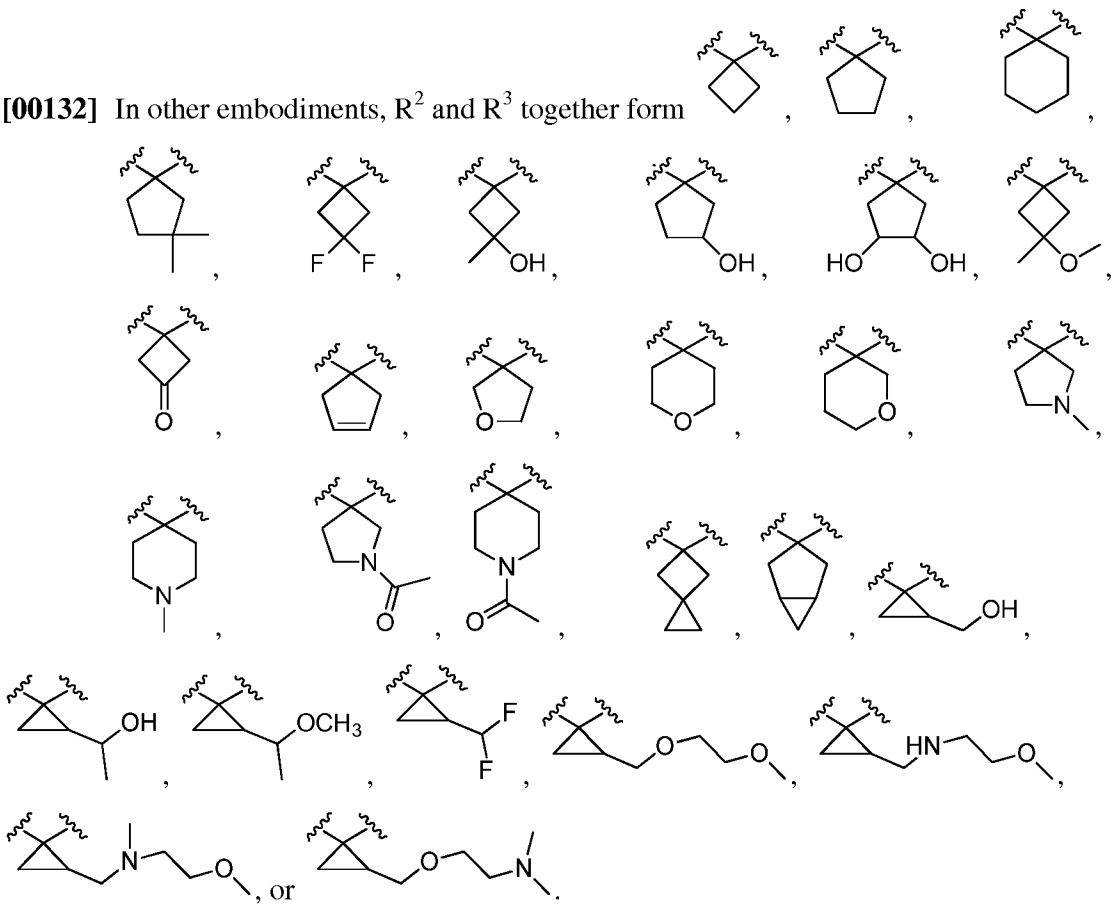
R^{4b}, R^{4c}, R^{4d} are each independently H, halo, optionally substituted alkyl or absent. In some of these embodiments, R^1 is optionally substituted phenyl. In some embodiments, the phenyl is unsubstituted. In other embodiments, the phenyl is substituted with a halogen.

[00129] In some embodiments, R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, carboxyl, and acetyl. In some exemplary embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of $C_{1\text{-}4}$ alkyl, $OC_{1\text{-}4}$ alkyl, OH, F, Cl, Br, amino, or carboxyl.

[00130] In some exemplary embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, carboxyl, acetyl, alkyl-OH, haloalkyl, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N($C_{1\text{-}4}$ alkyl), and n is 1 or 2.

[00131] For example, R^2 and R^3 together form a ring selected from any of the following formulas:



[00132] In other embodiments, R^2 and R^3 together form  , or .

[00133] In further embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

[00134] In other embodiments, R^2 and R^3 together form oxetane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, N-C_{1-2} alkyl azetidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylazetidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

[00135] In still other embodiments, R^2 and R^3 together form tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, OH, F, and Cl.

[00136] In yet other embodiments, R^2 and R^3 together form cyclobutanone, cyclopentanone, cyclohexanone, or cycloheptanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl. In some of these embodiments, R^2 and R^3 together form cyclobutanone, cyclopentanone, or cyclohexanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

[00137] In still other embodiments, R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[2.6]nonanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[3.6]decanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, spiro[4.6]undecanyl, spiro[5.5]undecanyl, spiro[5.6]dodecanyl, or spiro[6.6.]tridecanyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

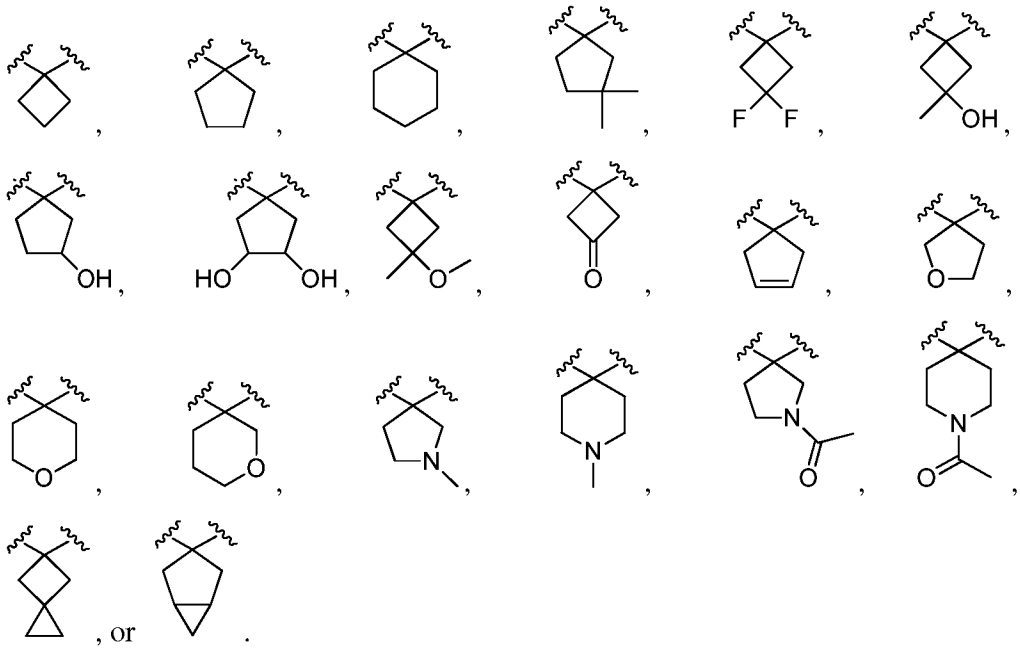
[00138] In some exemplary embodiments, R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

[00139] In yet other embodiments, R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[5.1.0]octyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[5.2.0]nonyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, bicyclo[5.3.0]decyl, bicyclo[4.4.0]decyl, bicyclo[5.4.0]undecyl, or bicyclo[5.5.0]dodecyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

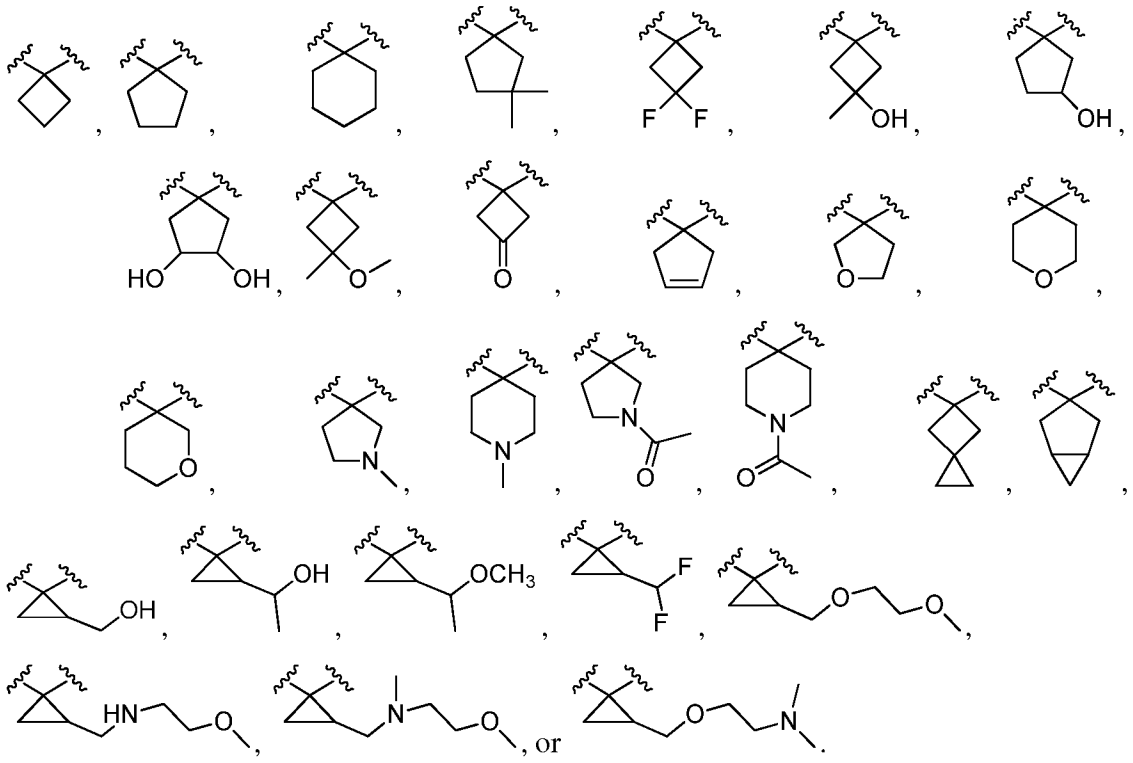
[00140] In some of these embodiments, R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, or bicyclo[4.4.0]decyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7,

OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

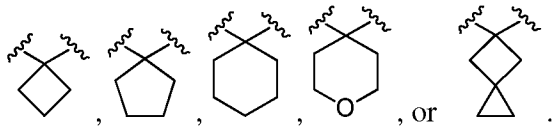
[00141] In some exemplary embodiments, R^2 and R^3 together form:



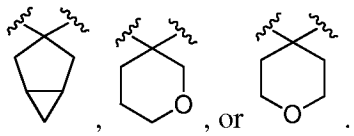
[00142] In other exemplary embodiments, R^2 and R^3 together form:



[00143] For example, R^2 and R^3 together form:



[00144] For example, R^2 and R^3 together form:



[00145] In some embodiments, R^2 and R^3 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted OC_{1-6} alkyl, CN, OH.

[00146] In some of these embodiments, R^2 and R^3 are each independently H, C_{1-4} alkyl, C_{3-6} cycloalkyl, OC_{1-4} alkyl, CN, or OH; wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and OC_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-2} alkyl, OC_{1-2} alkyl, OH, halogen, amino, and carboxyl.

[00147] In some exemplary embodiments, R^2 and R^3 are each independently H, C_{1-2} alkyl, OC_{1-3} alkyl, or OH; wherein each of the C_{1-2} alkyl and OC_{1-2} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, F, Cl, and Br. For example, R^2 and R^3 are each CH_3.

[00148] In one embodiment, R^1 is optionally substituted aryl. In a further embodiment, R^1 is optionally substituted alkyl. In a further embodiment, R^1 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00149] In one embodiment, R^1 is C_{2-6} alkenyl; wherein the C_{2-6} alkenyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

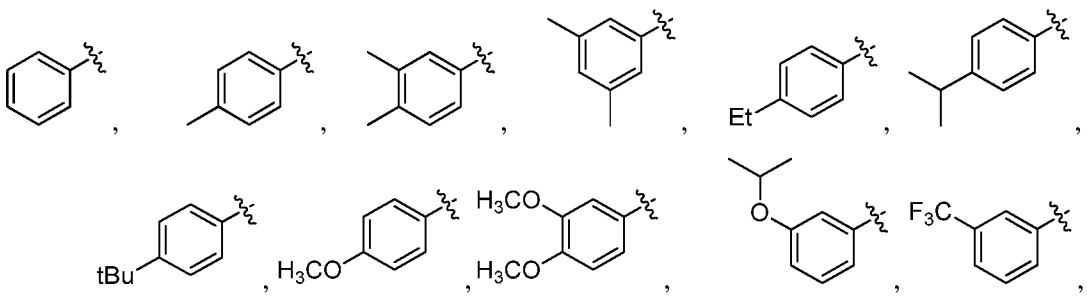
[00150] In one embodiment, R^1 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl. In some of these embodiments, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

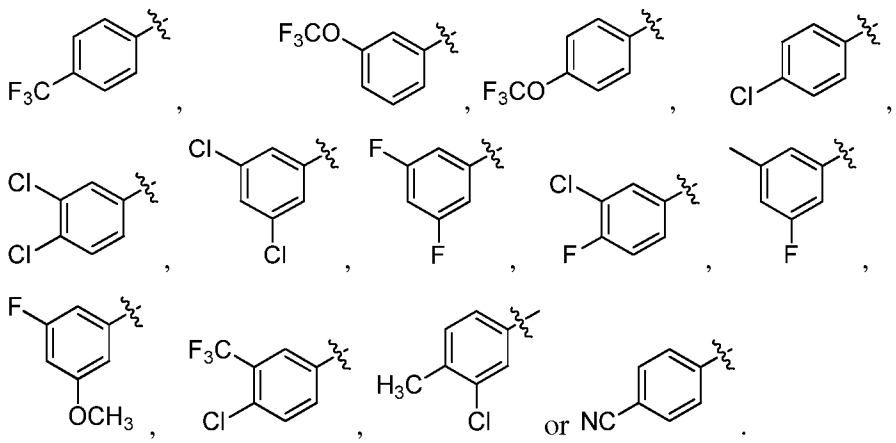
[00151] In a further embodiment, R^1 is cyclopentyl or cyclohexyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, fluoroalkyl hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen.

[00152] In one embodiment, R^1 is optionally substituted heterocyclyl. In a further embodiment, R^1 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

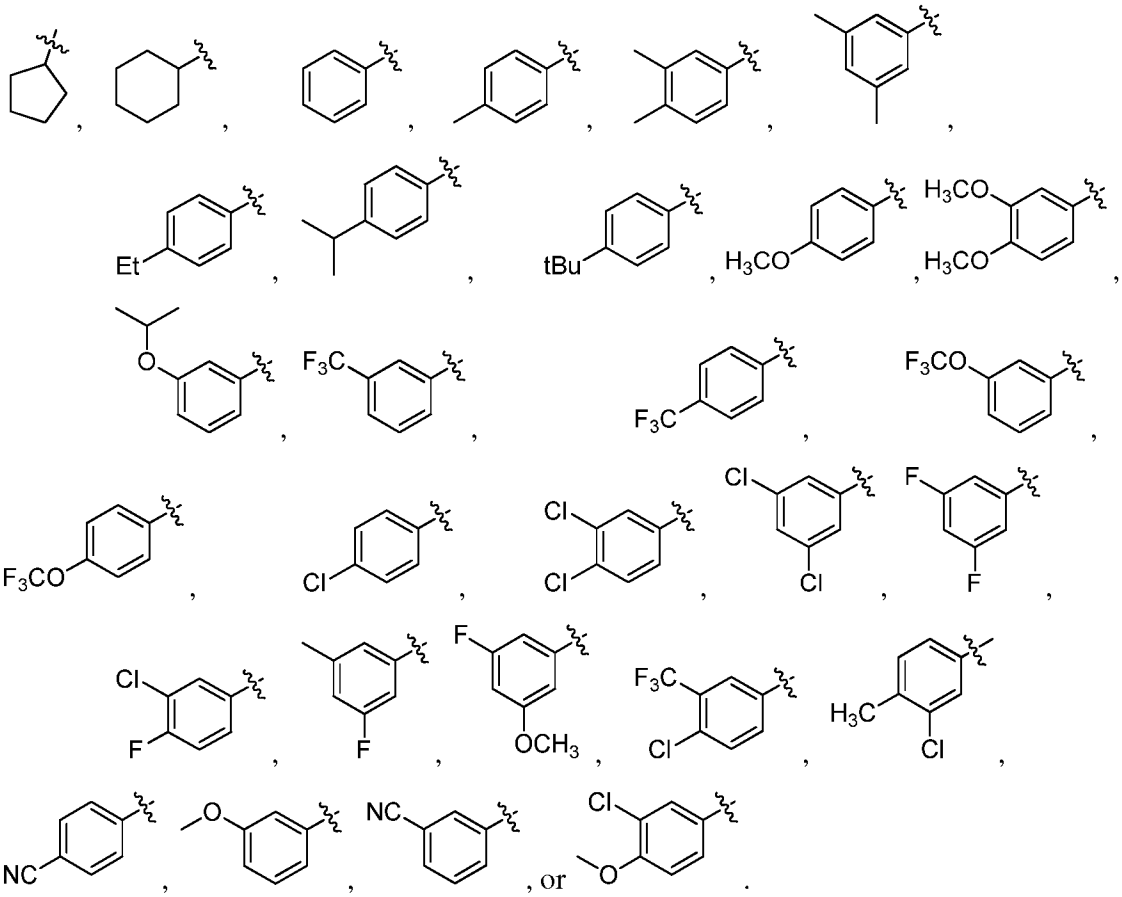
[00153] In one embodiment, R^1 is optionally substituted aryl or optionally substituted heteroaryl. In some of these embodiments, R^1 is pyrrole, furan, thiophene, isothiophene, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyridine, pyrimidine, or pyrazine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, haloalkoxyl, carboxyl, amino, and halogen. In some embodiments, R^1 is pyrrole, furan, thiophene, isothiophene, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyridine, pyrimidine, or pyrazine; wherein each of the foregoing moieties is optionally substituted with halogen. In some embodiments, R^1 is phenyl substituted with halogen. In some embodiments, R^1 is phenyl substituted with Cl, Br or F. In some embodiments, R^1 is phenyl substituted with Cl.

[00154] In an exemplary embodiment, R^1 is phenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN. In some exemplary embodiments, R^1 can include:

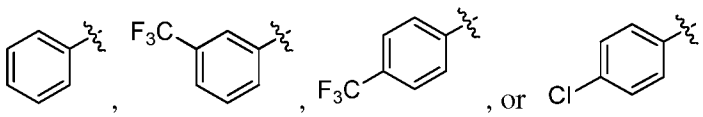




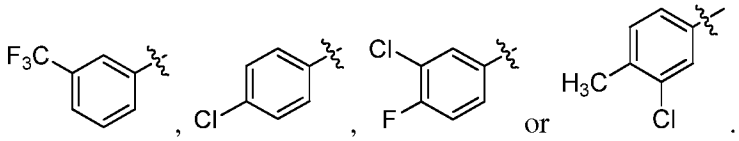
[00155] In some embodiments, R^1 is:



[00156] For example, R^1 is:



[00157] In another embodiment, R^1 is



[00158] In one embodiment:

A^1, A^2, and A^4 are each C; and

R^{4a}, R^{4b}, and R^{4d} are each H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

[00159] In some embodiments, R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl.

[00160] In some embodiments, R^5 is optionally substituted alkyl. In some of these embodiments, R^5 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00161] In some further embodiments, R^5 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane.

[00162] In some embodiments, R^5 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00163] In some embodiments, R^5 is optionally substituted alkylaryl.

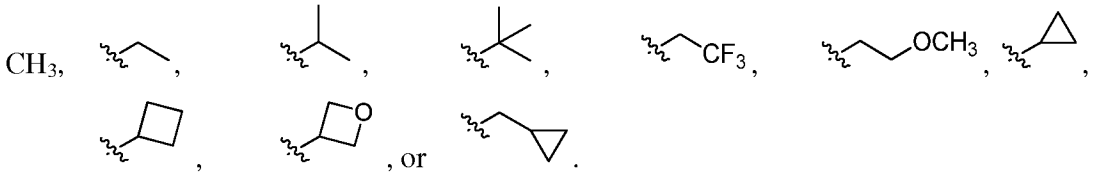
[00164] In some embodiments, R^5 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl. In some of these embodiments, R^5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00165] In some embodiments, R^5 is optionally substituted heterocyclyl. In some of these embodiments, R^5 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

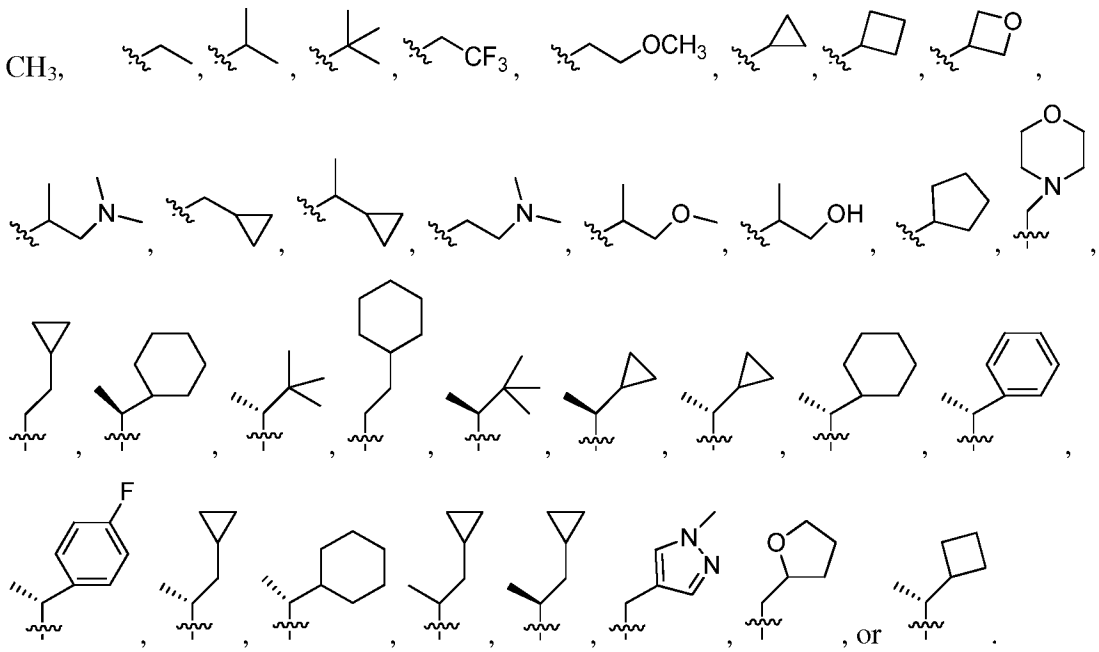
[00166] In some embodiments, R^5 is optionally substituted aralkyl, optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some of these embodiments, R^5 is benzyl optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some of these embodiments, R^5 is benzyl optionally substituted with halogen, for example Cl, F, or Br. In some of these embodiments, R^5 is benzyl optionally substituted with F.

[00167] In some embodiments, R^5 is optionally substituted heteroaralkyl optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some of these embodiments, R^5 is optionally substituted methylpyrazole, methylthiophene, methylpyrrole, methylfuran, methylindene, methylnaphthalene, methylpyridine, methylpyrimidine, or methylpyrazine, each independently optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. R^5 is optionally substituted methylpyrazole, methylthiophene, methylpyrrole, methylfuran, methylindene, methylnaphthalene, methylpyridine, methylpyrimidine, or methylpyrazine, each independently optionally substituted with $C_{1\text{-}4}$ alkyl. In some embodiments, R^5 is methylpyrazole, optionally substituted with one or more unsubstituted substituents selected from the group consisting of $C_{1\text{-}4}$ alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some embodiments, R^5 is methylpyrazole, optionally substituted with methyl.

[00168] In some of these embodiments, R^5 is



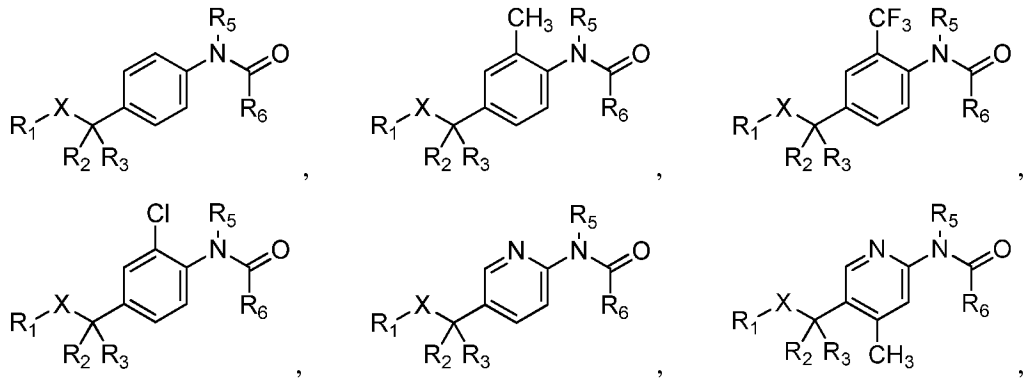
[00169] In some embodiments, R^5 can include:

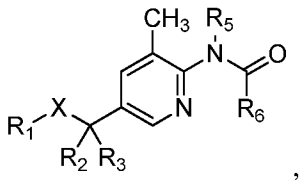
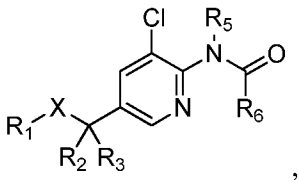
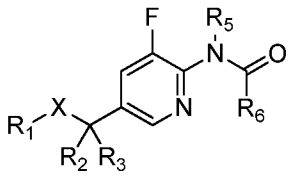
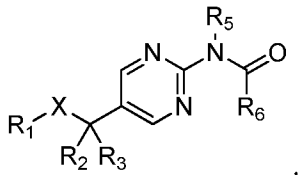


[00170] In some embodiments, X is SO.

[00171] In other embodiments, X is SO_2.

[00172] In some embodiments, the compound of Formula I includes a structure selected from the group below:



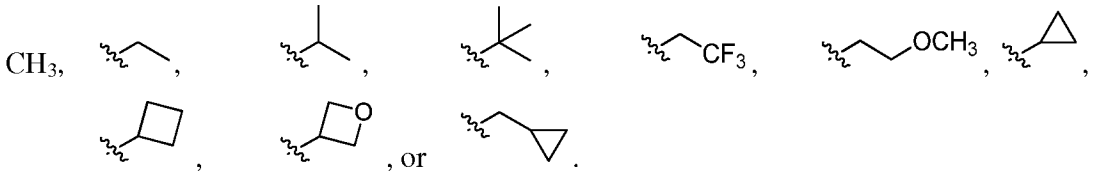
and ..

[00173] In each of the foregoing structures, R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl. In some of these embodiments, R^5 is optionally substituted alkyl. In some of these embodiments, R^5 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some further embodiments, R^5 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane.

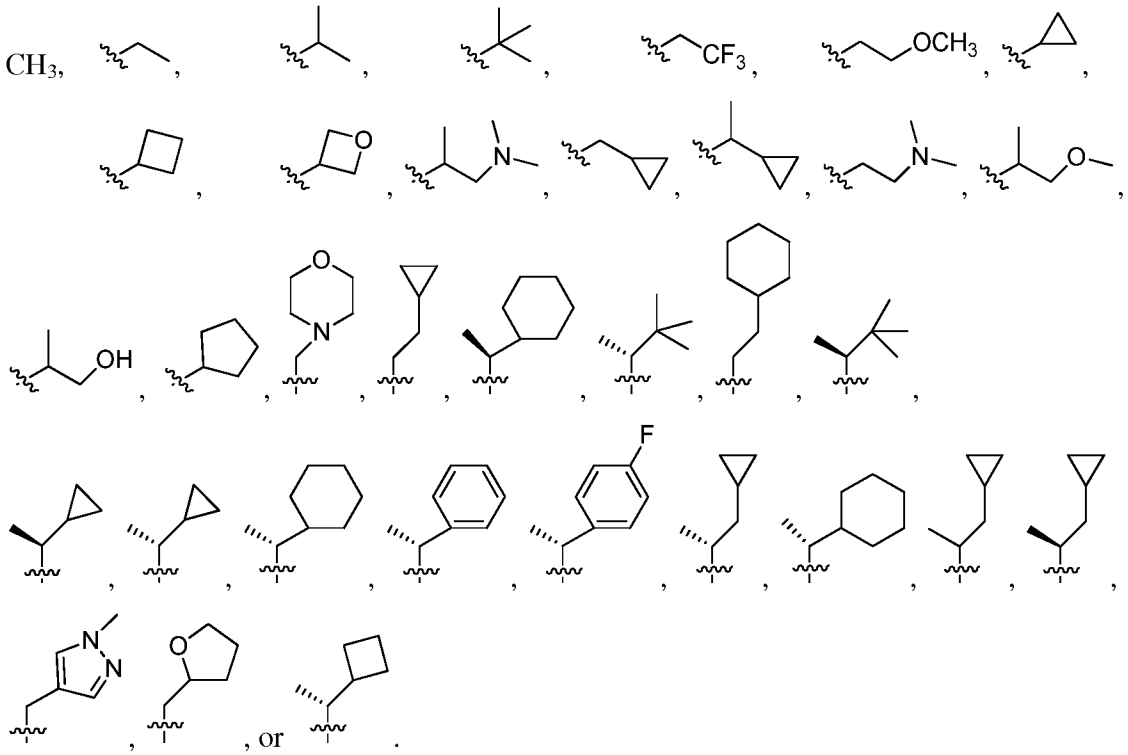
[00174] In one embodiment, R^5 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some embodiments, R^5 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl. In some of these embodiments, R^5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00175] In some embodiments, R^5 is optionally substituted heterocyclyl. In some of these embodiments, R^5 can include aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents

selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some exemplary embodiments, R^5 can include:



In some embodiments, R^5 can include:



[00176] In each of the foregoing structures, R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted alkoxyl.

[00177] In each of the foregoing structures, R^6 is optionally substituted alkyl. In some of these embodiments, R^6 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In other embodiments, R^6 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane. In one embodiment, R^6 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted

substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In one embodiment, R^6 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

[00178] In some of these embodiments, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl or a C_{6-10} bicyclic cycloalkyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

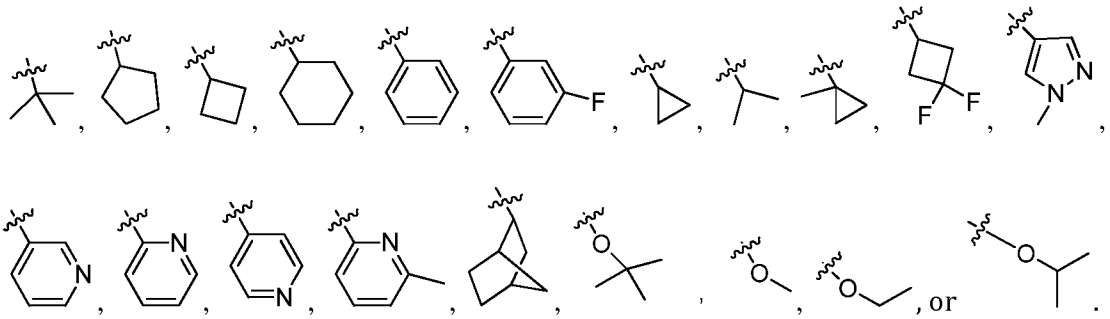
[00179] In some embodiments, R^6 is optionally substituted heterocyclyl. In these embodiments, R^6 can include aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

[00180] In some embodiments, R^6 is optionally substituted aryl or optionally substituted heteroaryl. In some of these embodiments, R^6 is pyrrole, furan, thiophene, isothiophene, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyridine, pyrimidine, pyrazole, or pyrazine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen. In some exemplary embodiments, R^6 is phenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN. In some embodiments, R^6 is pyridine that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN. For example R^6 can include tert-butyl, cyclobutane, cyclopentane, or cyclohexane. In some embodiments, R^6 is H.

[00181] In some of these embodiments, R^6 is alkoxyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen. In some exemplary embodiments, R^6 is C_{1-4} alkoxyl selected from the group

consisting of methoxy, methoxymethylpropane, methoxypropane, ethoxy, propyloxy and butoxy, each independently optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen.

[00182] In each of the foregoing structures, R^6 is:



[00183] In each of the foregoing structures, X is SO.

[00184] In each of the foregoing structures, X is SO_2.

[00185] In a further embodiment, the invention is directed to a compound of Formula I or pharmaceutically acceptable salts thereof, wherein:

X is SO_2;

A^1 and A^4 are each C;

A^2 and A^3 are each independently C or N;

R^1 is phenyl, optionally substituted with a group selected from halogen and C_{1-4}alkyl wherein the alkyl is optionally substituted with halogen;

R^2 and R^3 together form an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted C_{1-6}alkyl, halogen, or absent when the ring atom to which they are attached is N;

R^5 is optionally substituted C_{1-6}alkyl or optionally substituted carbocyclyl;

R^6 is optionally substituted C_{1-6}alkyl, or optionally substituted carbocyclyl, or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[00186] In another embodiment, the invention is directed to a compound of Formula I, Formula Ia, Formula Ib, or pharmaceutically acceptable salts thereof, wherein:

[00187] X is SO_2;

[00188] A^1 and A^4 are each C;

[00189] A^2 and A^3 are each independently C or N;

[00190] R^1 is phenyl optionally substituted with a group selected from halogen, CH_3 and CF_3;

[00191] R^2 and R^3 together form a 6 membered heterocyclyl or a 6 membered carbocyclyl;

[00192] R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, C_{1-4}alkyl, halogen, or absent;

[00193] R^5 is optionally substituted C_{1-6}alkyl or optionally substituted carbocyclyl;

[00194] R^6 is optionally substituted C_{1-4}alkyl, or C_{1-7}carbocyclyl.

[00195] In another embodiment, the invention is directed to a compound of Formula I, Formula Ia, or pharmaceutically acceptable salts thereof, wherein:

[00196] X is SO_2;

[00197] A^1 and A^4 are each C;

[00198] A^2 and A^3 are each independently C or N;

[00199] R^1 is phenyl optionally substituted with a group selected from halogen, CH_3 and CF_3;

[00200] R^2 and R^3 together form a pyranyl or a 6 membered bicyclic carbocyclyl;

[00201] R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, C_{1-4}alkyl, halogen, or absent;

[00202] R^5 is optionally substituted C_{1-6}alkyl or optionally substituted carbocyclyl;

[00203] R^6 is optionally substituted C_{1-4}alkyl, or C_{1-7}carbocyclyl.

[00204] In another embodiment, the invention is directed to a compound of Formula I or pharmaceutically acceptable salts thereof, wherein:

[00205] X is SO_2;

[00206] A^1 and A^4 are each C;

[00207] A^2 and A^3 are each independently C or N;

[00208] R^1 is phenyl optionally substituted with a group selected from halogen, CH_3 and CF_3;

[00209] R^2 and R^3 together form a pyranyl or a 6 membered bicyclic carbocyclyl;

[00210] R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, halogen or absent;

[00211] R^5 is optionally substituted C_{1-6}alkyl or optionally substituted carbocyclyl;

[00212] R^6 is optionally substituted C_{1-4}alkyl, or C_{1-7}carbocyclyl.

[00213] In some embodiments, R^2 and R^3 together form an optionally substituted monocyclic carbocyclyl or a monocyclic heterocyclyl; and X is S, SO or SO_2; and A^1, A^2, A^3, A^4, $R^{1,}$ R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^5, and R^6 are defined as in Formula I. In still further embodiments, one of A^1 and A^4 is nitrogen and A^2, A^3, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^5, and R^6 are defined as in Formula I.

[00214] In still further embodiments, one of A^1 and A^2 is nitrogen and A^2, A^3, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^5, and R^6 are defined as in Formula I.

[00215] In some embodiments, R^{4a} is H and A^1, A^2, A^3, A^4, R^1, R^2, R^3, R^{4b}, R^{4c}, R^{4d}, R^5, and R^6 are defined as in Formula I.

[00216] In some embodiments, R^{4d} is H and A^1, A^2, A^3, A^4, R^1, R^2, R^3, R^{4b}, R^{4c}, R^{4a}, R^5, and R^6 are defined as in Formula I.

[00217] In some embodiments, R^6 is a C_2-C_5 alkyl and A^1, A^2, A^3, A^4, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^5 are defined as in Formula I.

[00218] In some embodiments, R^6 is amino, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted heterocyclyl, and A^1, A^2, A^3, A^4, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^5 are defined as in Formula I.

[00219] In a further embodiment, the invention is directed to a compound of Formula I or pharmaceutically acceptable salts thereof, wherein:

X is SO_2;

A^1 and A^4 are each independently C or N;

A^2 and A^3 are each independently C or N;

R^1 is phenyl, optionally substituted with a group selected from halogen and C_{1-4} alkyl wherein the C_{1-4} alkyl is optionally substituted with halogen;

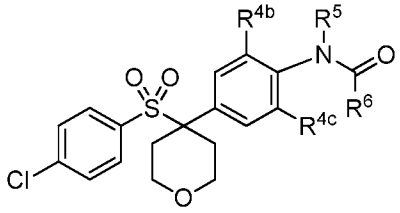
R^2 and R^3 together form a cycloaliphatic or heterocycloalkyl each of which is independently unsubstituted or substituted with one or more of C_{1-6} alkyl, C_{1-6} alkoxyl, halogen, oxo, hydroxyl, carboxyl, acetyl, C_{1-6} alkyl-OH, C_{1-6} haloaliphatic, amino, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted C_{1-6} alkyl, halogen, or absent when the ring atom to which they are attached is N;

R^5 is optionally substituted C_{1-6} alkyl, optionally substituted heterocycloalkyl, or optionally substituted cycloalkyl;

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, or optionally substituted C_{1-6} alkoxyl;

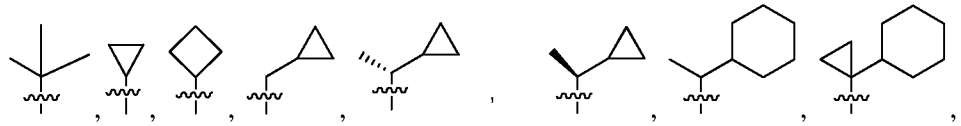
[00220] In one embodiment, the invention is directed to a compound of Formula Ia or pharmaceutically acceptable salts thereof, wherein the compound of Formula Ia has the structure:

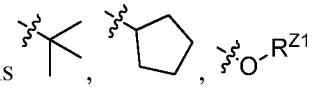
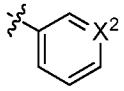


wherein:

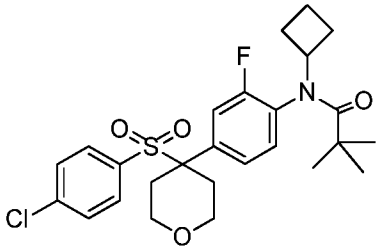
R^{4b} is F or Cl;

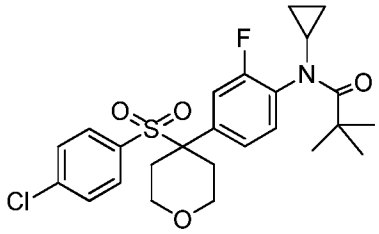
R^{4c} is H, F, Cl, or methoxy;

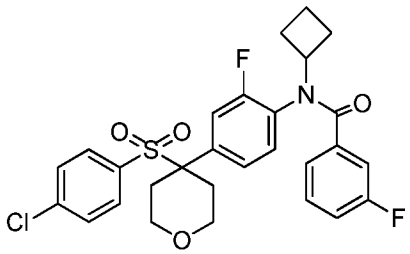
R^5 is  , wherein X_1 is CH_2, or O; and

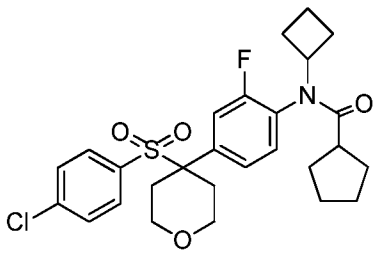
R^6 is  , wherein R^{Z1} is alkyl , or  , wherein X^2 is CR^{Z2} or N, and R^{Z2} is an alkyl, H or F. In one embodiment, X^2 is CR^{Z2}.

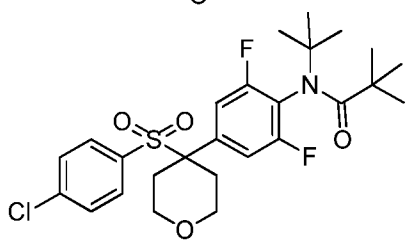
[00221] In some embodiments of the above formula, the compound can be:

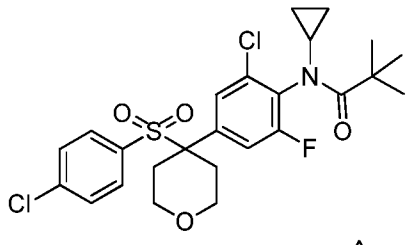
152 

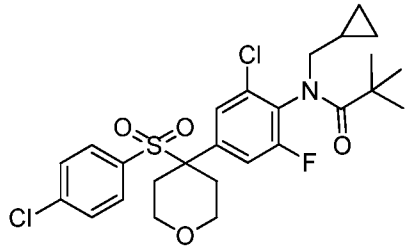
153 

162 

163 

169 

177 

180 

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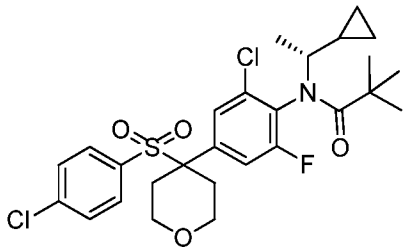

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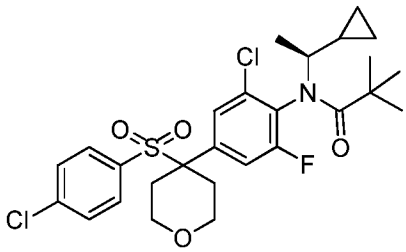
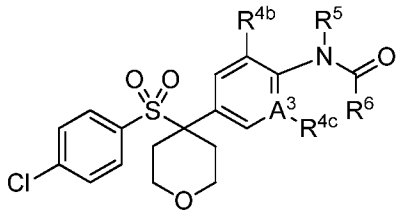


or a pharmaceutically acceptable salt thereof.

[00222] In one embodiment, the invention is directed to a compound of Formula Ia or pharmaceutically acceptable salts thereof, wherein the compound of Formula Ia has the structure:



or a pharmaceutically acceptable salt thereof,

wherein:

A^3 is C or N;

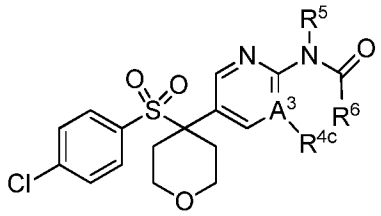
R^{4b} is F or Cl;

R^{4c} is H, F, Cl, methoxy or absent when A^3 is N;

R^5 is optionally substituted C_{3-6} cycloalkyl, optionally substituted 3 to 7 membered heterocycloalkyl, optionally substituted C_{7-16} aralkyl, optionally substituted 6 to 10 membered heteroaralkyl, or C_{1-6} alkyl optionally substituted with one to four of C_{1-6} cycloalkyl, C_{6-8} aryl, or 3 to 7 membered heterocycloalkyl, each of the foregoing substituents may be independently unsubstituted or substituted with one or more of C_{1-4} alkyl or halogen; and

R^6 is C_{1-6} alkyl, C_{3-10} cycloalkyl, 4 to 7 membered heteroaryl, C_{6-14} aryl, or C_{1-6} alkoxyl, wherein each of the foregoing moieties is independently unsubstituted or substituted with one or more of C_{1-4} alkyl or halogen.

[00223] In one embodiment, the invention is directed to a compound of Formula Ia or pharmaceutically acceptable salts thereof, wherein the compound of Formula Ia has the structure:



or a pharmaceutically acceptable salt thereof,

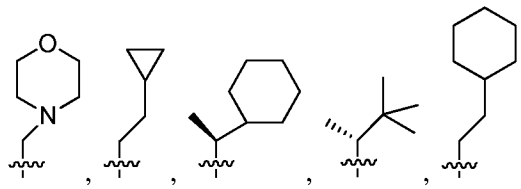
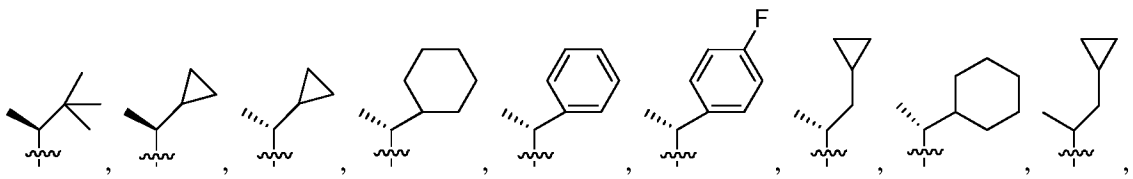
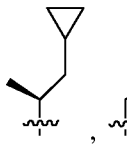
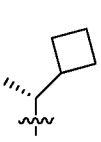
wherein:

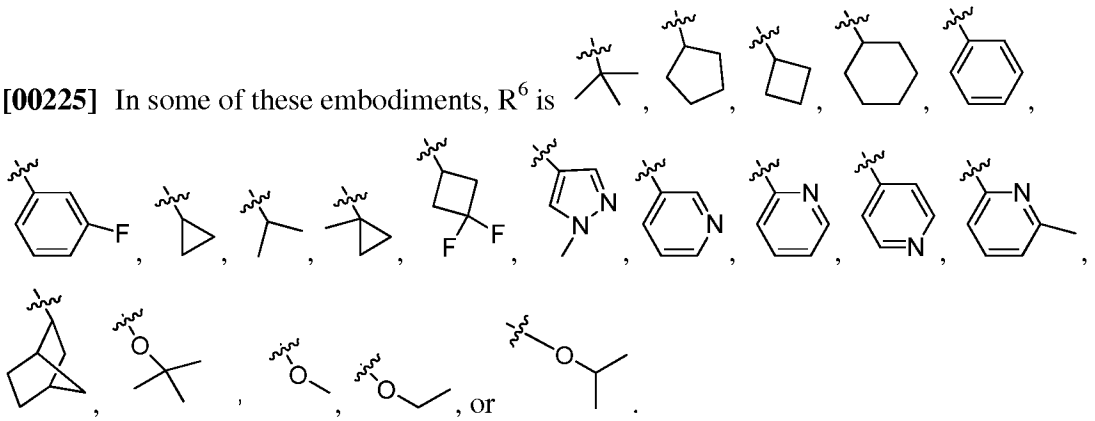
A^3 is C or N;

R^{4b} is F or Cl;

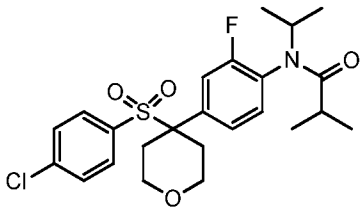
R^{4c} is H, F, Cl, methoxy or absent when A^3 is N;

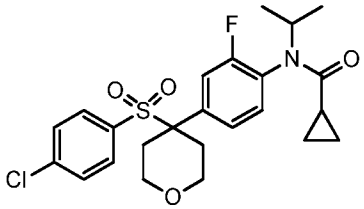
R^5 is optionally substituted C_{3-6} cycloalkyl, optionally substituted 3 to 7 membered heterocycloalkyl, or C_{1-6} alkyl optionally substituted with one to four of C_{1-6} cycloalkyl, C_{6-14} aryl, or 3 to 7 membered heterocycloalkyl, each of the foregoing substituents may be independently unsubstituted or substituted with one or more of C_{1-4} alkyl or halogen; and R^6 is C_{1-6} alkyl, C_{3-10} cycloalkyl, 4 to 7 membered heteroaryl, C_{6-14} aryl, or C_{1-6} alkoxyl, wherein each of the foregoing moieties is independently unsubstituted or substituted with one or more of C_{1-4} alkyl or halogen.

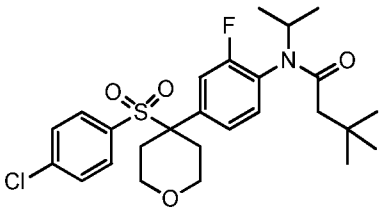
[00224] In some of these embodiments, R^5 is  ,  ,  , or  .

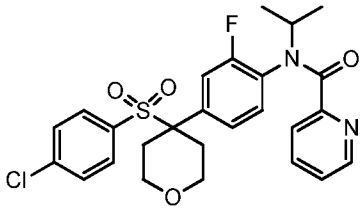
[00225] In some of these embodiments, R^6 is  .

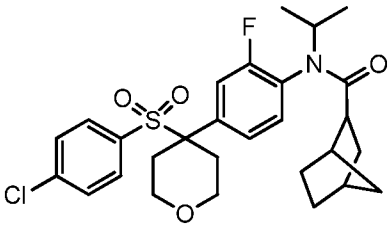
[00226] In some embodiments of the above formula, the compound can be:

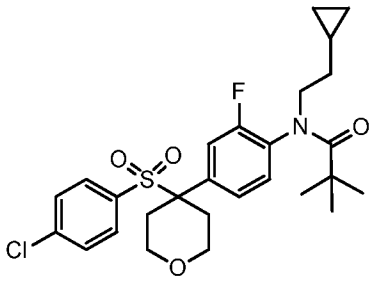
197 

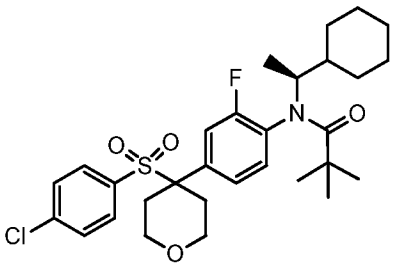
198 

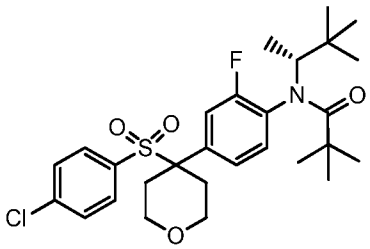
201 

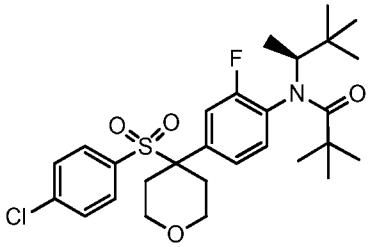
204 

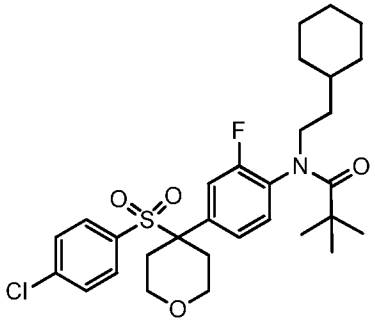
207 

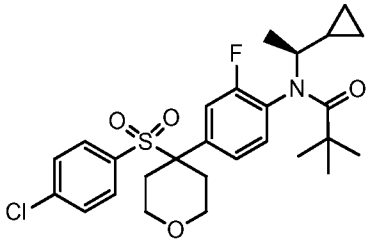
210 

211 

212 

213 

214 

216 

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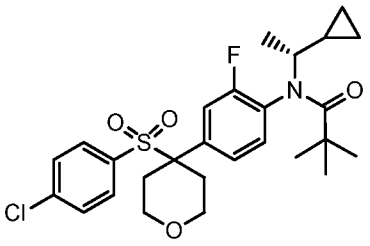

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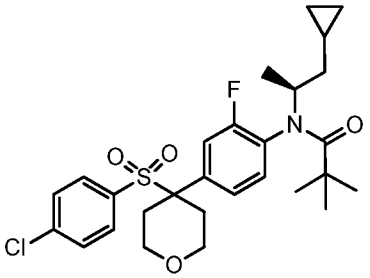

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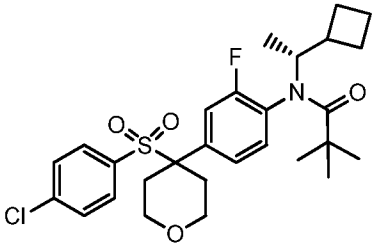

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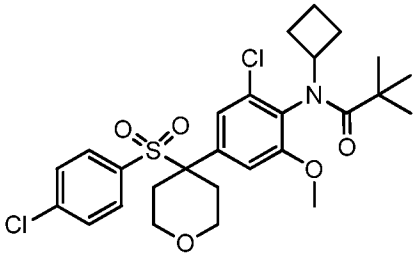

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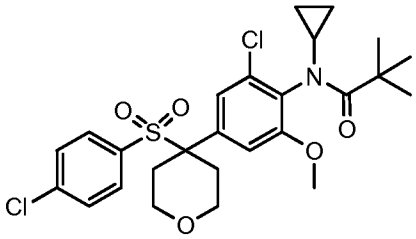

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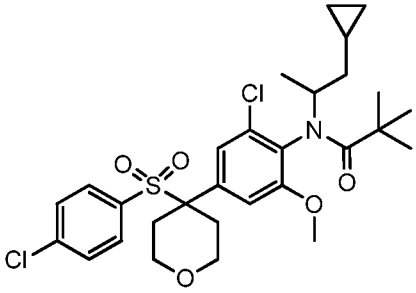
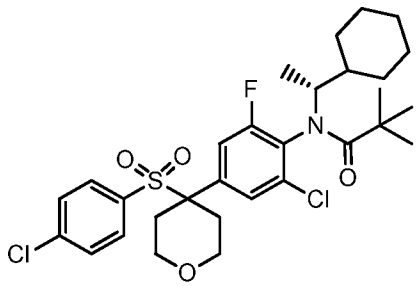


227



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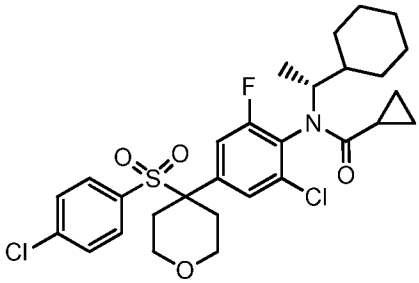
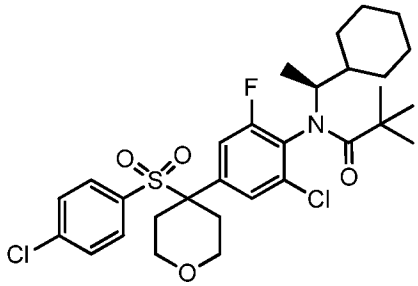
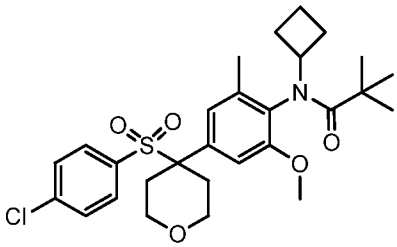


229



232



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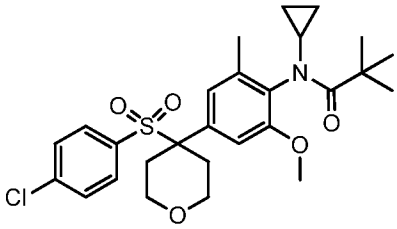

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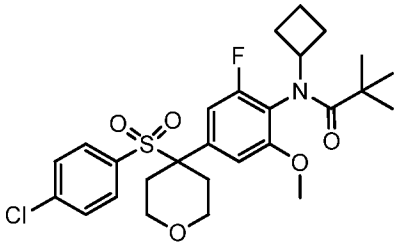
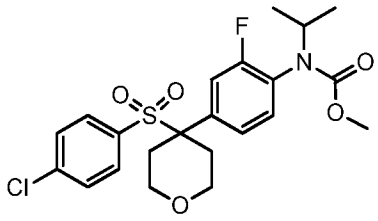
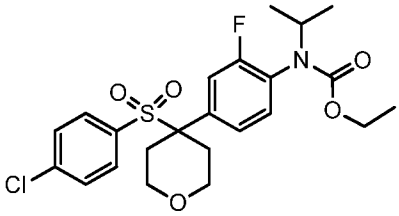


238



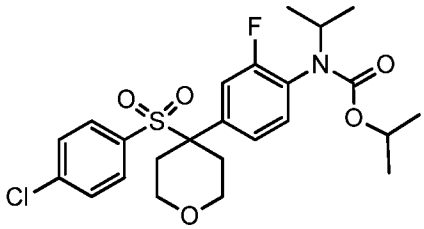
methyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

239



ethyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

240

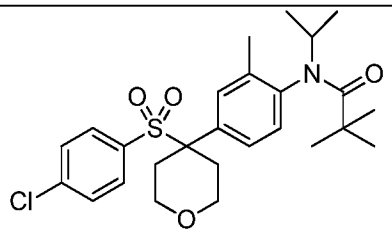


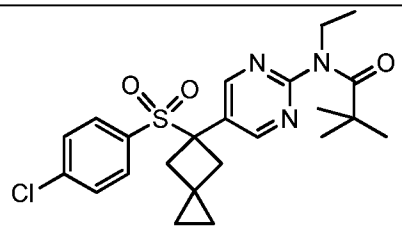
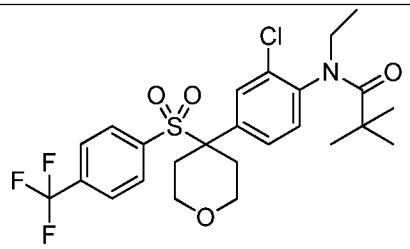
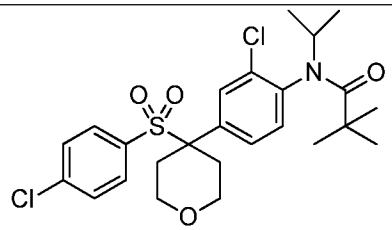
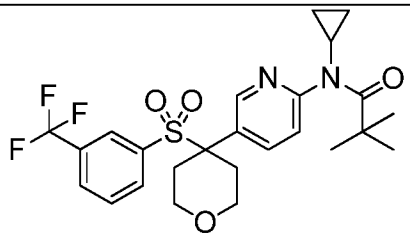
isopropyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

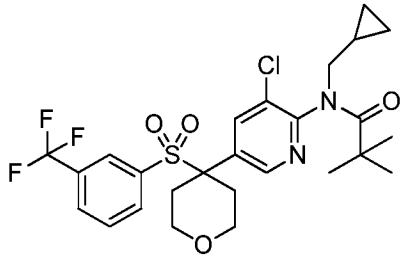
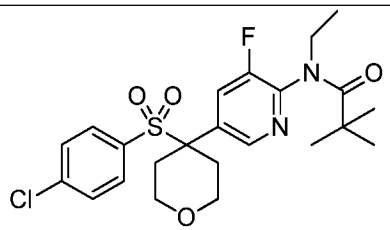
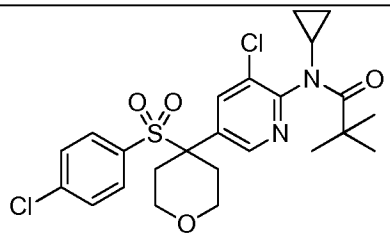
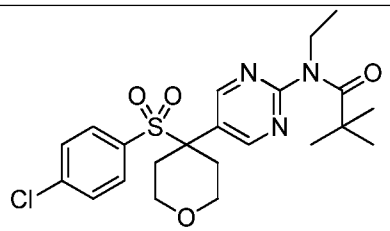
or a pharmaceutically acceptable salt thereof.

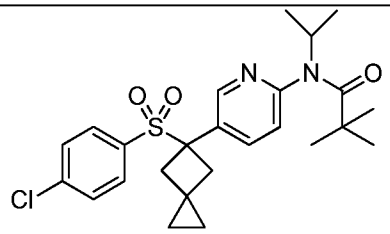
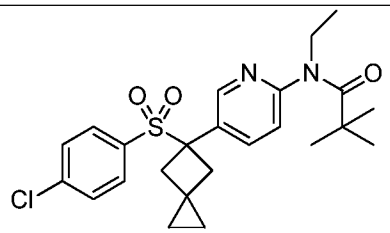
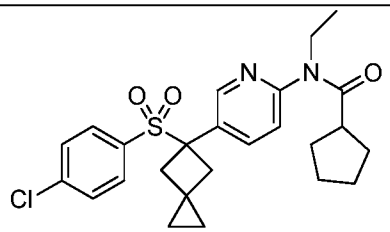
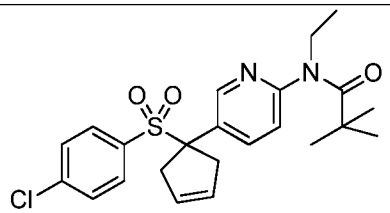
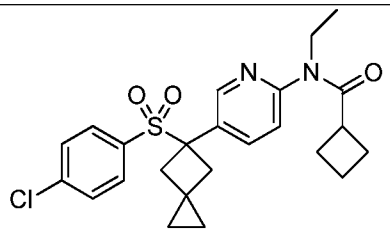
[00227] For example, the compound of Formula I can be a compound as shown in Table 1 or a pharmaceutically acceptable salt thereof. Exemplary Embodiments of the Compound of Formula I.

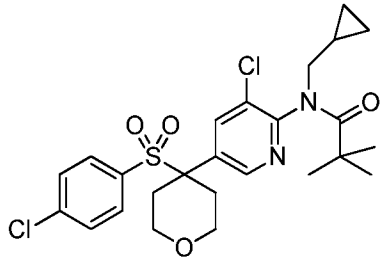
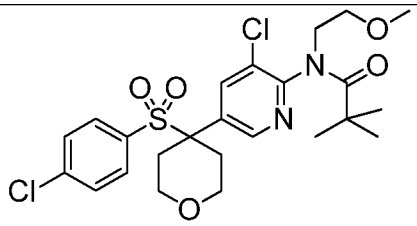
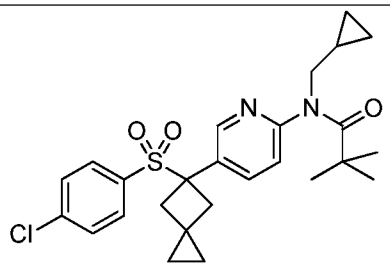
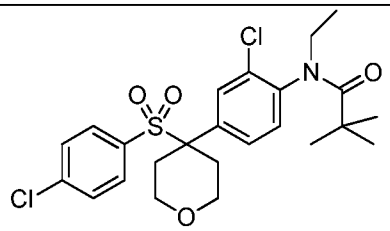
Table 1. Exemplary Embodiments of the Compound of Formula I

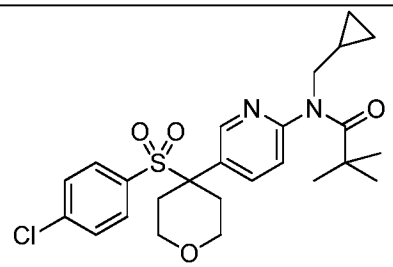
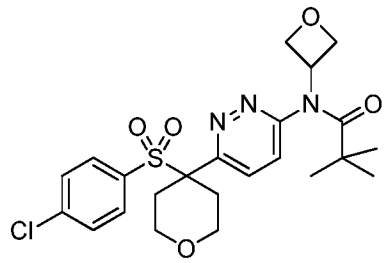
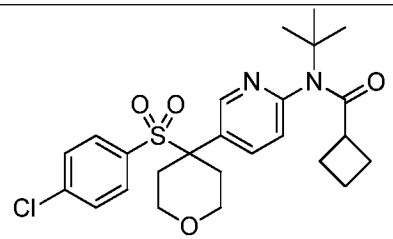
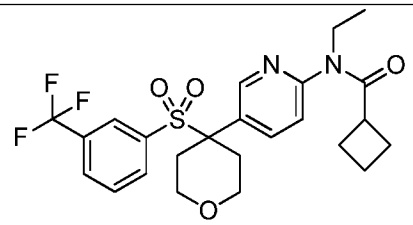
Ex #	Structure
1	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-isopropylpivalamide

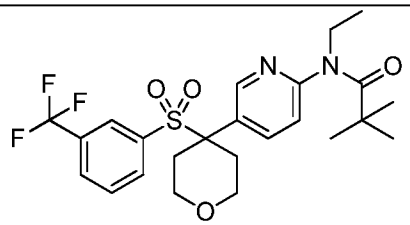
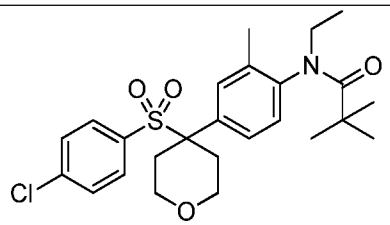
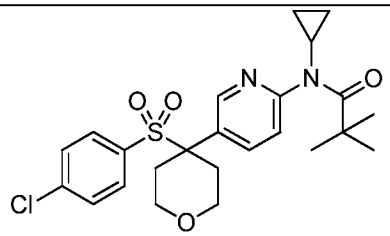
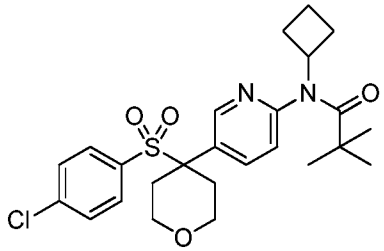
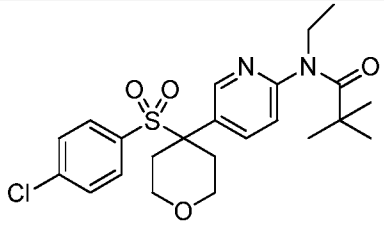
Ex #	Structure
2	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyrimidin-2-yl)-*N*-ethylpivalamide
3	 *N*-(2-chloro-4-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-ethylpivalamide
4	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
5	 *N*-cyclopropyl-*N*-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)pivalamide

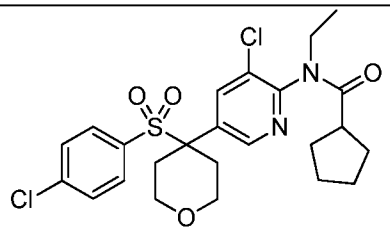
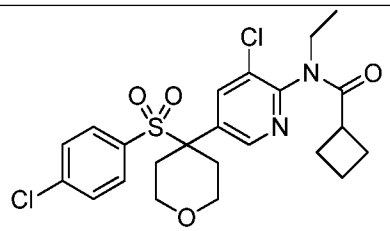
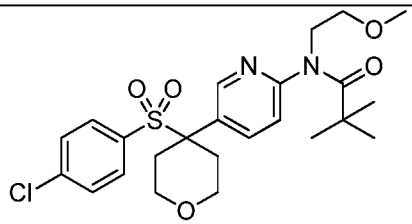
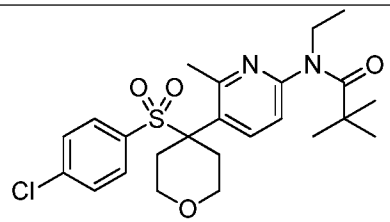
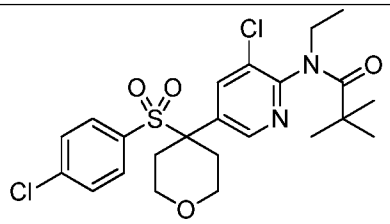
Ex #	Structure
6	 *N*-(3-chloro-5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-(cyclopropylmethyl)pivalamide
7	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-ethylpivalamide
8	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-cyclopropylpivalamide
9	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyrimidin-2-yl)-*N*-ethylpivalamide

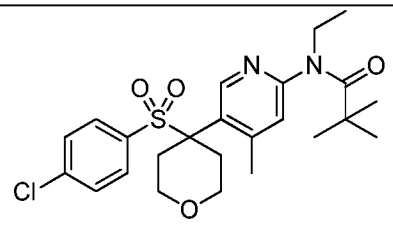
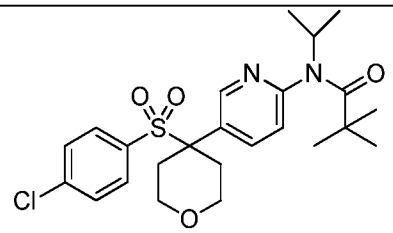
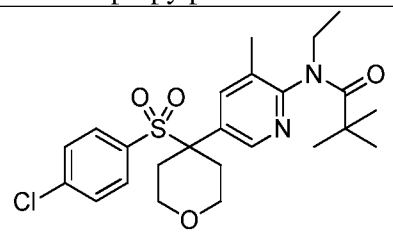
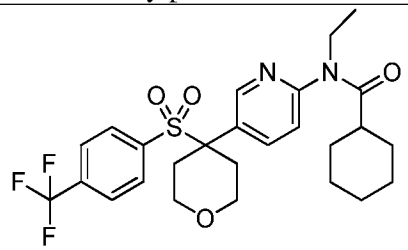
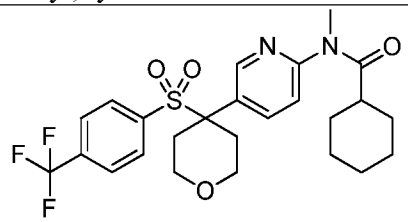
Ex #	Structure
10	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-*N*-isopropylpivalamide
11	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-*N*-ethylpivalamide
12	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-*N*-ethylcyclopentanecarboxamide
13	 *N*-(5-(1-((4-chlorophenyl)sulfonyl)cyclopent-3-en-1-yl)pyridin-2-yl)-*N*-ethylpivalamide
14	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-*N*-ethylcyclobutanecarboxamide

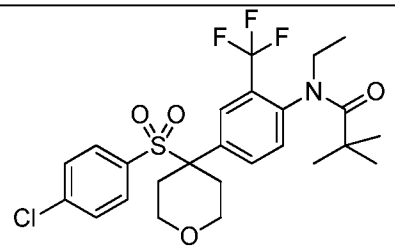
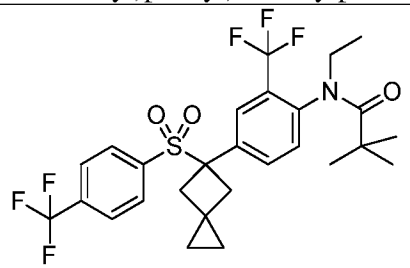
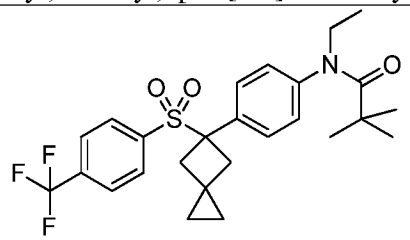
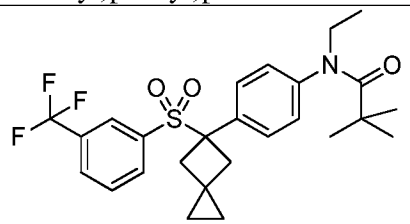
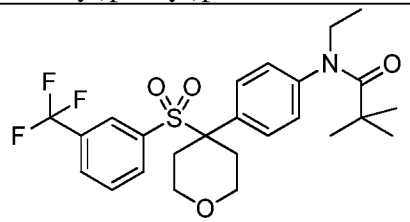
Ex #	Structure
15	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl) pyridin-2-yl)-*N*-(cyclopropylmethyl)pivalamide
16	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-(2-methoxyethyl)pivalamide
17	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-*N*-(cyclopropylmethyl)pivalamide
18	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-ethylpivalamide

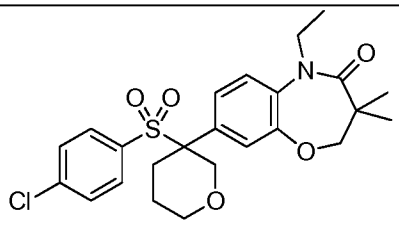
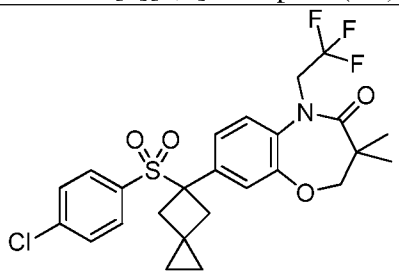
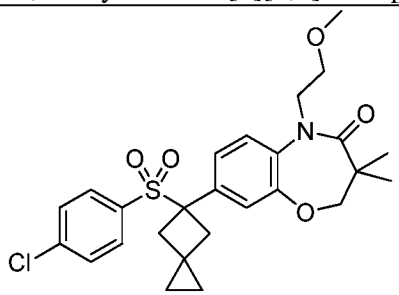
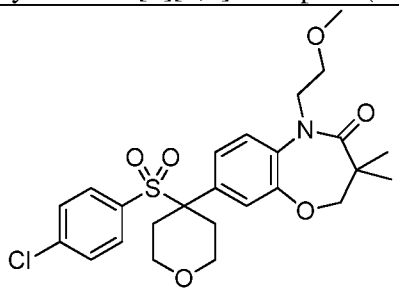
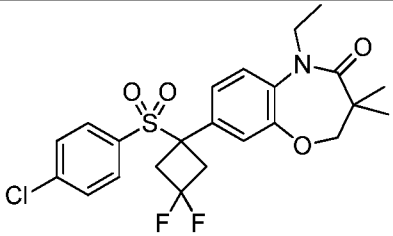
Ex #	Structure
19	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-(cyclopropylmethyl)pivalamide
20	 *N*-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridazin-3-yl)-*N*-(oxetan-3-yl)pivalamide
21	 *N*-(*tert*-butyl)-*N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl) pyridin-2-yl)cyclobutanecarboxamide
22	 *N*-ethyl-*N*-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)cyclobutanecarboxamide

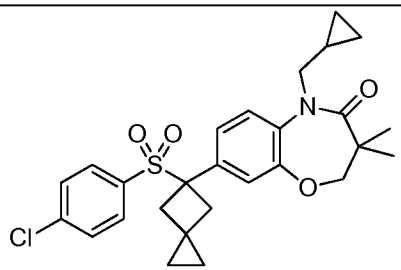
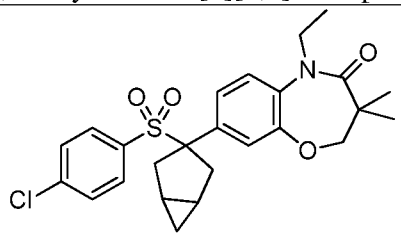
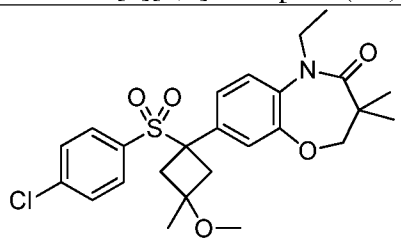
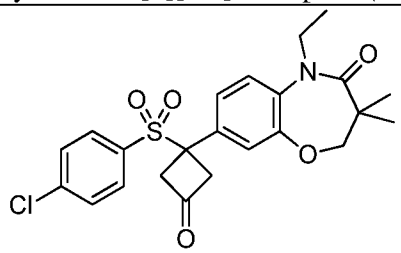
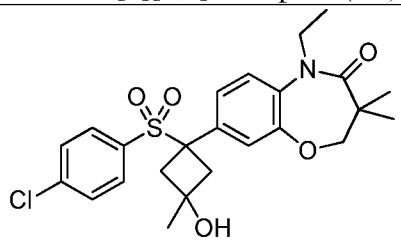
Ex #	Structure
23	 *N*-ethyl-*N*-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)pivalamide
24	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-ethylpivalamide
25	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-cyclopropylpivalamide
26	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-cyclobutylpivalamide
27	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-ethylpivalamide

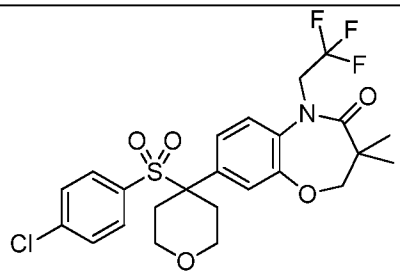
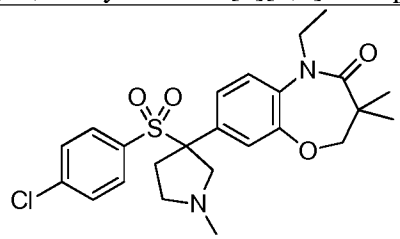
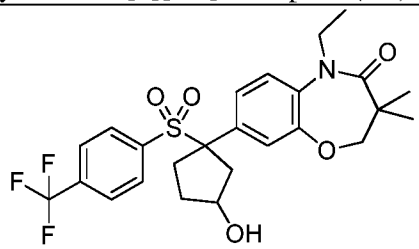
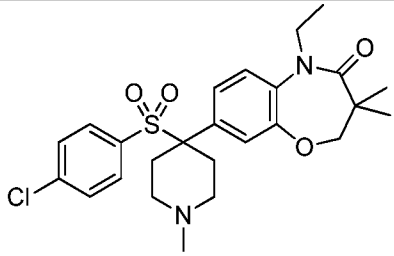
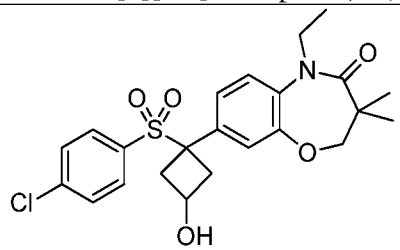
Ex #	Structure
28	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-ethylcyclopentanecarboxamide
29	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl) pyridin-2-yl)-*N*-ethylcyclobutanecarboxamide
30	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-*N*-(2-methoxyethyl)pivalamide
31	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methylpyridin-2-yl)-*N*-ethylpivalamide
32	 *N*-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl) -*N*-ethylpivalamide

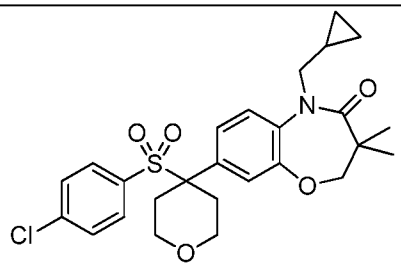
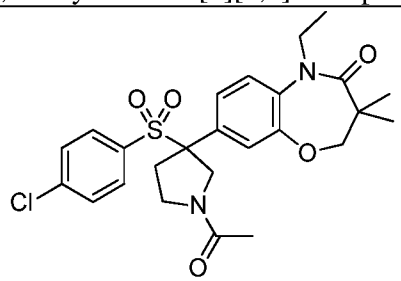
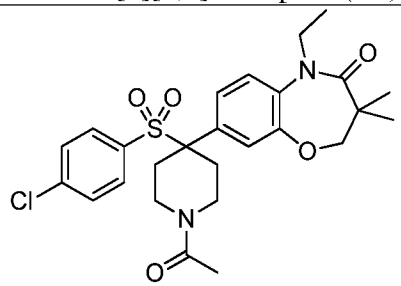
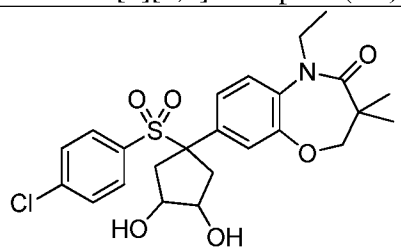
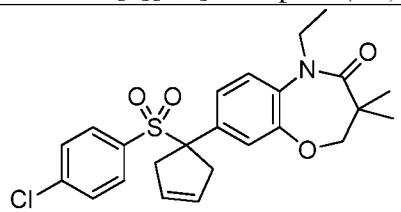
Ex #	Structure
33	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-4-methylpyridin-2-yl)-*N*-ethylpivalamide
34	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-isopropylpivalamide
35	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-3-methylpyridin-2-yl)-N-ethylpivalamide
36	 N-ethyl-N-(5-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclohexanecarboxamide
37	 N-methyl-N-(5-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclohexanecarboxamide

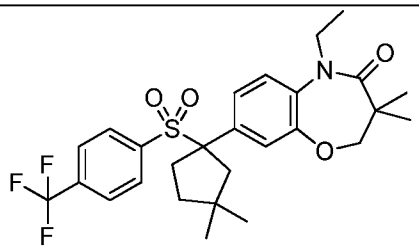
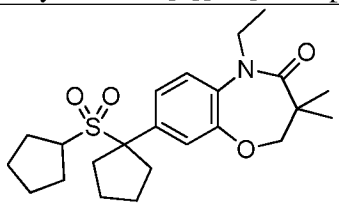
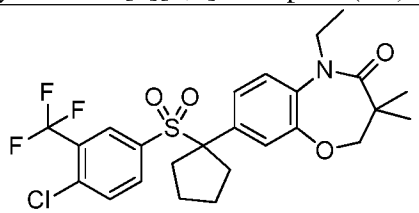
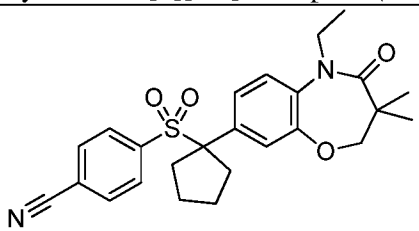
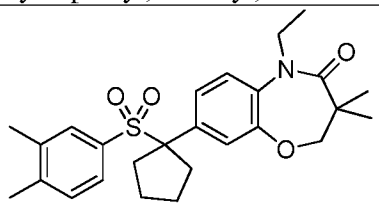
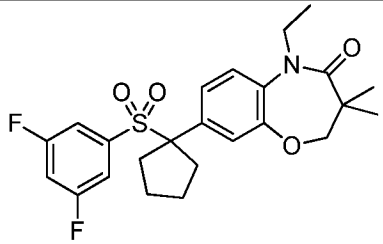
Ex #	Structure
38	 N-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenyl)-N-ethylpivalamide
39	 N-ethyl-N-(2-(trifluoromethyl)-4-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
40	 N-ethyl-N-(4-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
41	 N-ethyl-N-(4-(5-((3-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
42	 N-ethyl-N-(4-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)phenyl)pivalamide

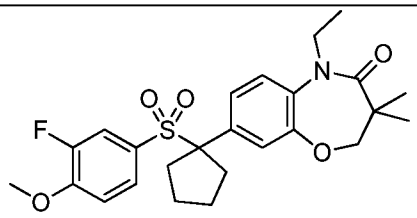
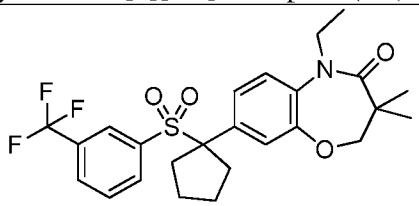
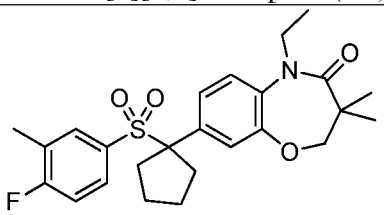
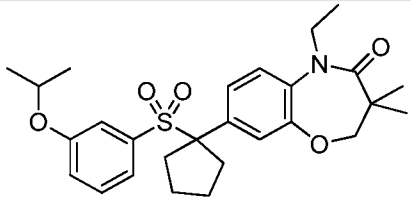
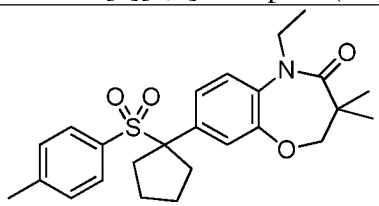
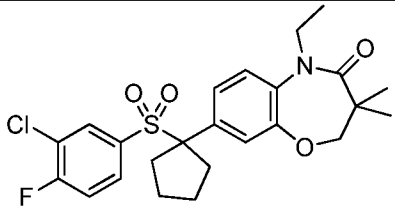
Ex #	Structure
43	 8-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
44	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-3,3-dimethyl-5-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
45	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-5-(2-methoxyethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
46	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-(2-methoxyethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
47	 8-(1-((4-chlorophenyl)sulfonyl)-3,3-difluorocyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

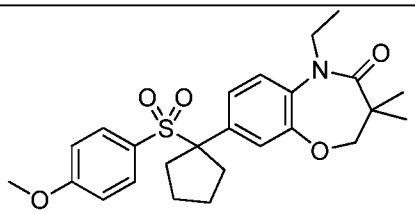
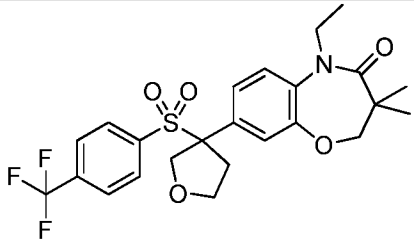
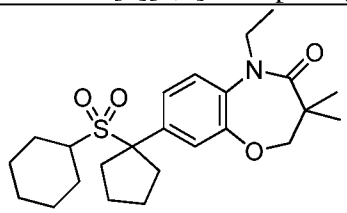
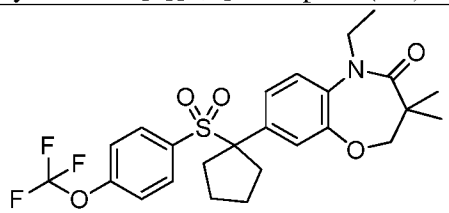
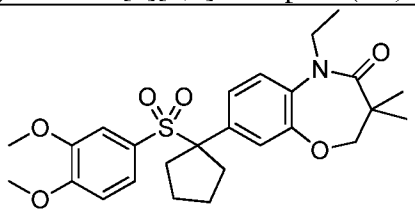
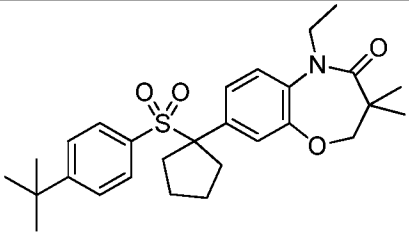
Ex #	Structure
48	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-5-(cyclopropylmethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
49	 8-(3-((4-chlorophenyl)sulfonyl)bicyclo[3.1.0]hexan-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
50	 8-(1-((4-chlorophenyl)sulfonyl)-3-methoxy-3-methylcyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
51	 8-(1-((4-chlorophenyl)sulfonyl)-3-oxocyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
52	 8-(1-((4-chlorophenyl)sulfonyl)-3-hydroxy-3-methylcyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

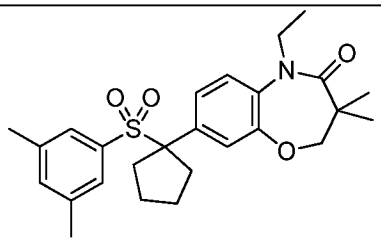
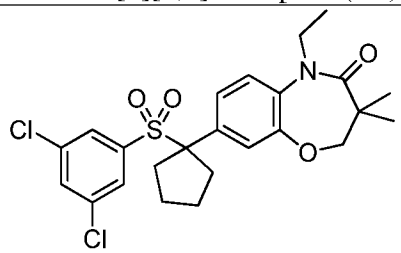
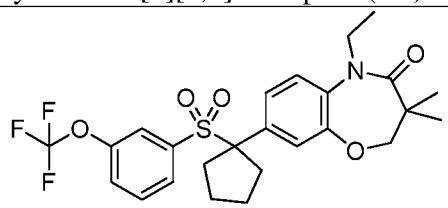
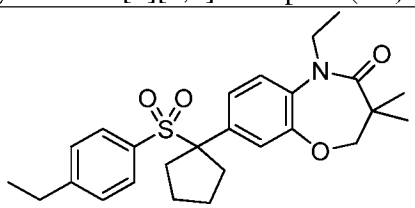
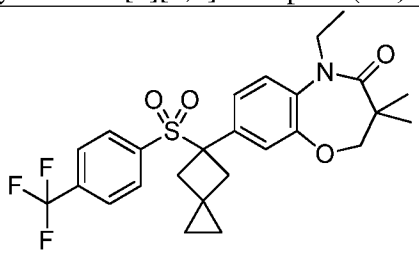
Ex #	Structure
53	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-3,3-dimethyl-5-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
54	 8-(3-((4-chlorophenyl)sulfonyl)-1-methylpyrrolidin-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
55	 5-ethyl-8-(3-hydroxy-1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
56	 8-(4-((4-chlorophenyl)sulfonyl)-1-methylpiperidin-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
57	 8-(1-((4-chlorophenyl)sulfonyl)-3-hydroxycyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

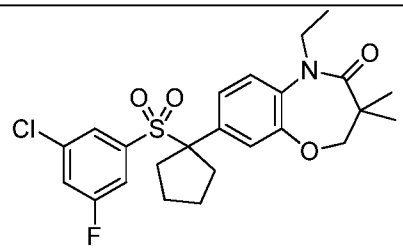
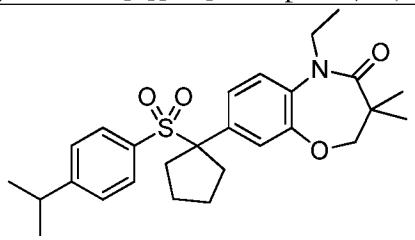
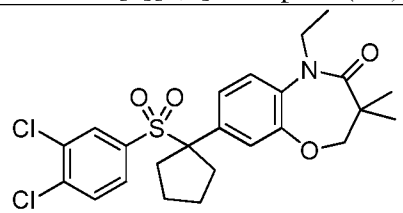
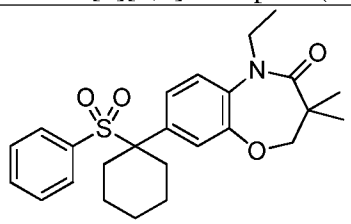
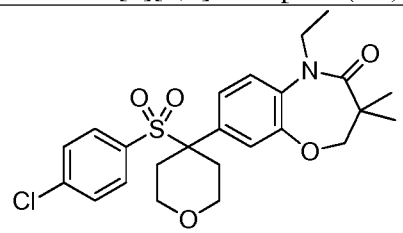
Ex #	Structure
58	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-(cyclopropylmethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
59	 8-(1-acetyl-3-((4-chlorophenyl)sulfonyl)pyrrolidin-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
60	 8-(1-acetyl-4-((4-chlorophenyl)sulfonyl)piperidin-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
61	 8-(1-((4-chlorophenyl)sulfonyl)-3,4-dihydroxycyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
62	 8-(1-((4-chlorophenyl)sulfonyl)cyclopent-3-en-1-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

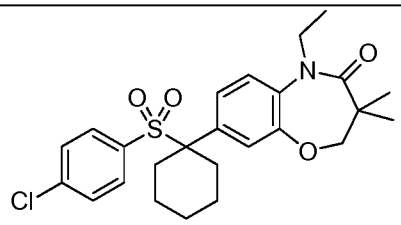
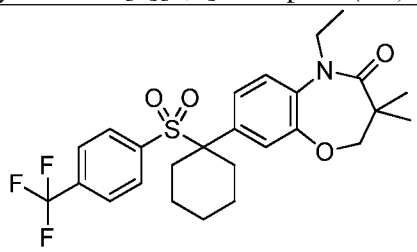
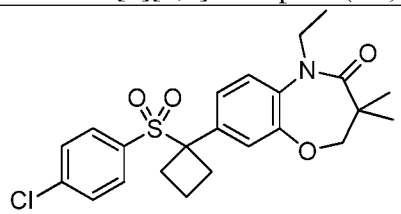
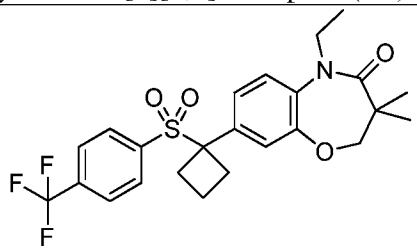
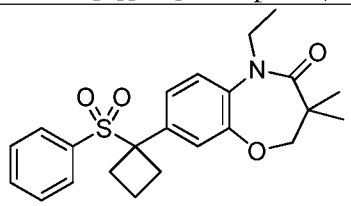
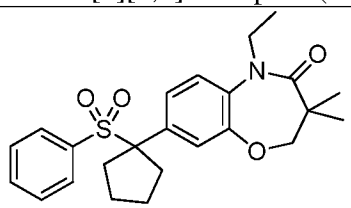
Ex #	Structure
63	 8-(3,3-dimethyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
64	 8-(1-(cyclopentylsulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
65	 8-(1-((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
66	 4-((1-(5-ethyl-3,3-dimethyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-8-yl)cyclopentyl)sulfonyl)benzonitrile
67	 8-(1-((3,4-dimethylphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
68	 8-(1-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

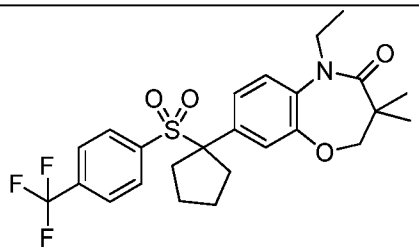
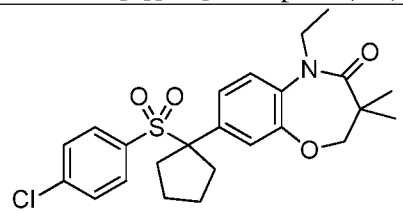
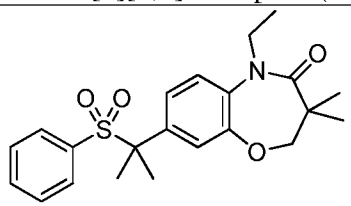
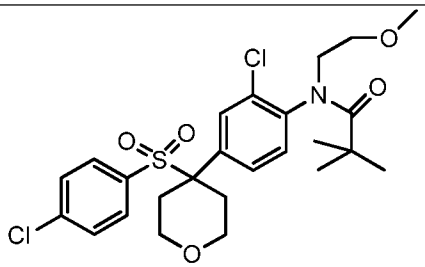
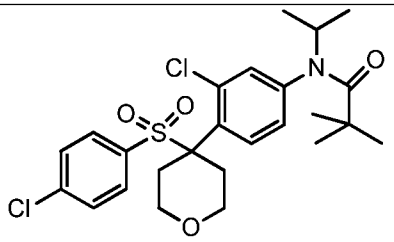
Ex #	Structure
69	 5-ethyl-8-(1-((3-fluoro-4-methoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
70	 5-ethyl-3,3-dimethyl-8-(1-((3-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
71	 5-ethyl-8-(1-((4-fluoro-3-methylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
72	 5-ethyl-8-(1-((3-isopropoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
73	 5-ethyl-3,3-dimethyl-8-(1-tosylcyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
74	 8-(1-((3-chloro-4-fluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

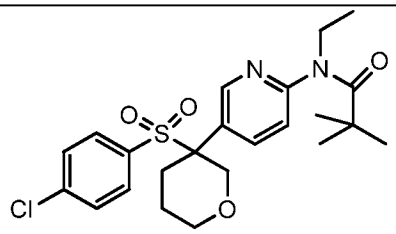
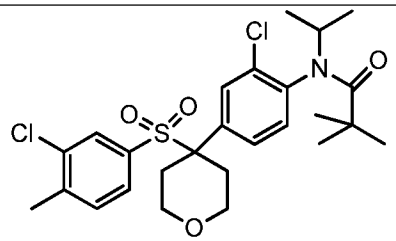
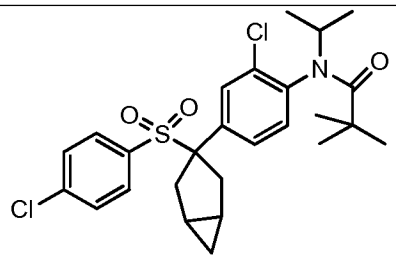
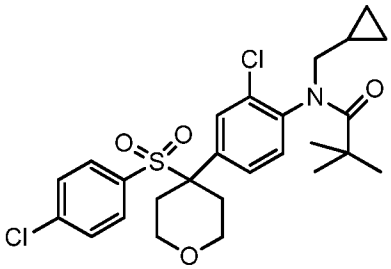
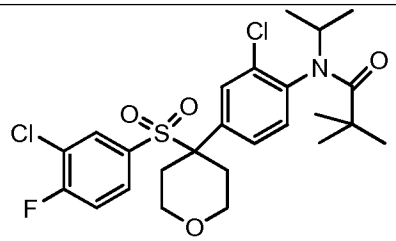
Ex #	Structure
75	 5-ethyl-8-(1-((4-methoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
76	 5-ethyl-3,3-dimethyl-8-(3-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydrofuran-3-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
77	 8-(1-(cyclohexylsulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
78	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
79	 8-(1-((3,4-dimethoxyphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
80	 8-(1-((4-(tert-butyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

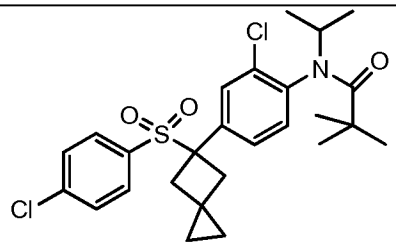
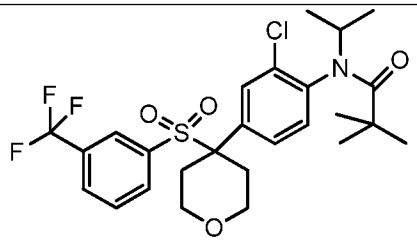
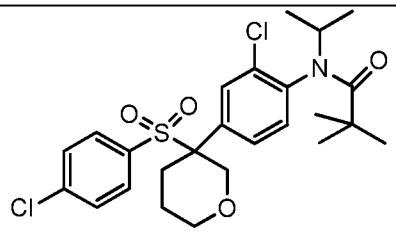
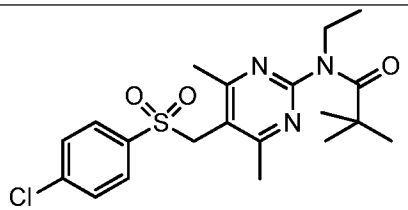
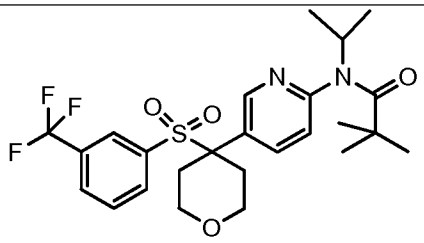
Ex #	Structure
81	 8-(1-((3,5-dimethylphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
82	 8-(1-((3,5-dichlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
83	 5-ethyl-3,3-dimethyl-8-(1-((3-(trifluoromethoxy)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
84	 5-ethyl-8-(1-((4-ethylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
85	 5-ethyl-3,3-dimethyl-8-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

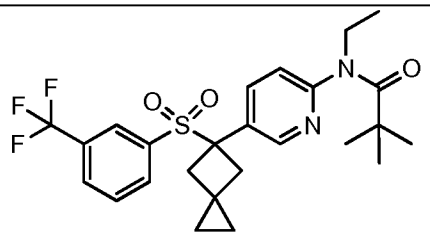
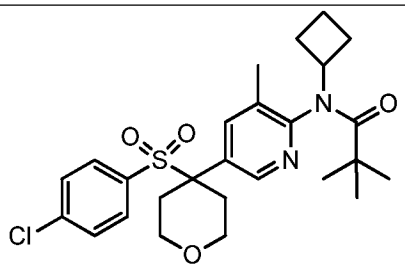
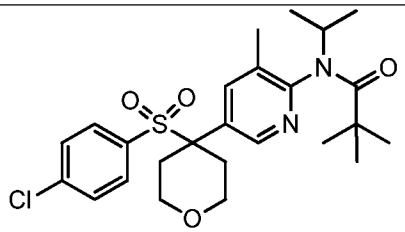
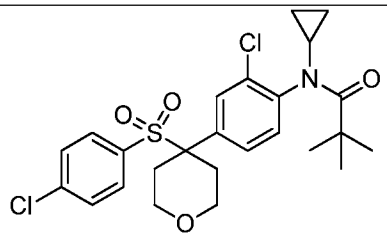
Ex #	Structure
86	 8-(1-((3-chloro-5-fluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
87	 5-ethyl-8-(1-((4-isopropylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
88	 8-(1-((3,4-dichlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
89	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclohexyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
90	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

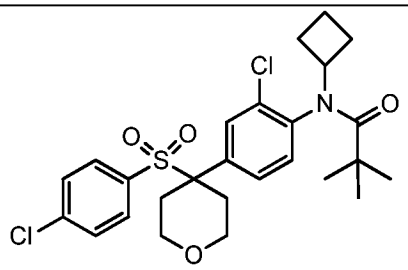
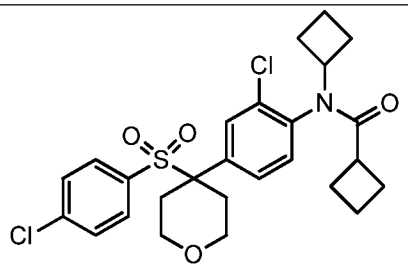
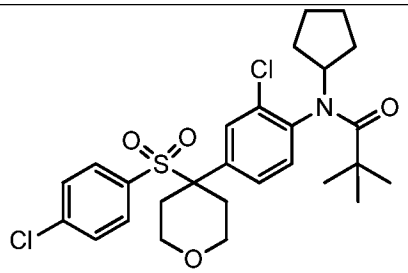
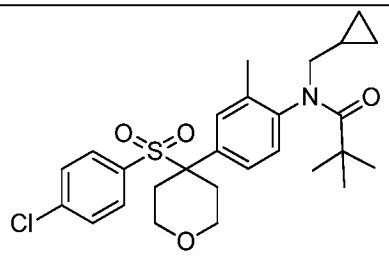
Ex #	Structure
91	 8-(1-((4-chlorophenyl)sulfonyl)cyclohexyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
92	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclohexyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
93	 8-(1-((4-chlorophenyl)sulfonyl)cyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
94	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
95	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclobutyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
96	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

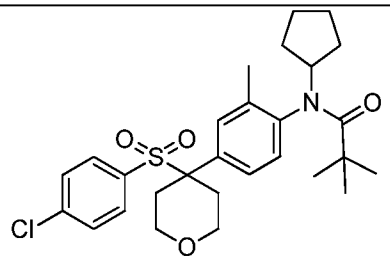
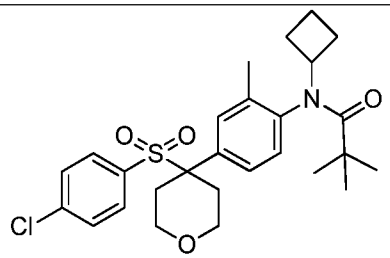
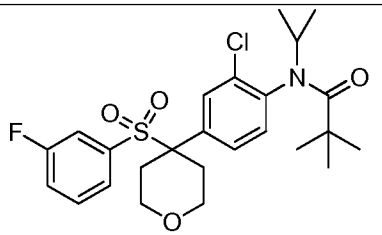
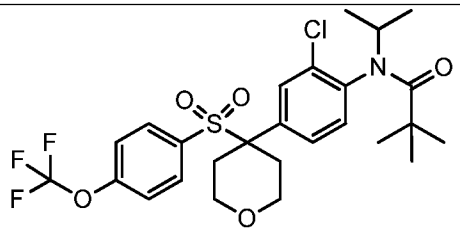
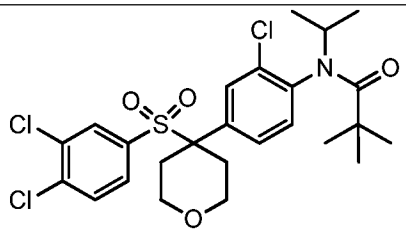
Ex #	Structure
97	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
98	 8-(1-((4-chlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
99	 5-ethyl-3,3-dimethyl-8-(2-(phenylsulfonyl)propan-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
100	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-(2-methoxyethyl)pivalamide
101	 *N*-(3-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

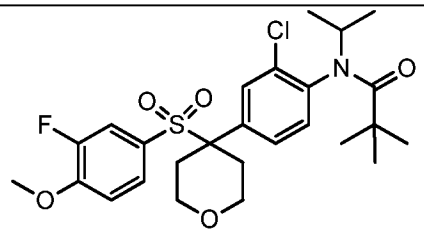
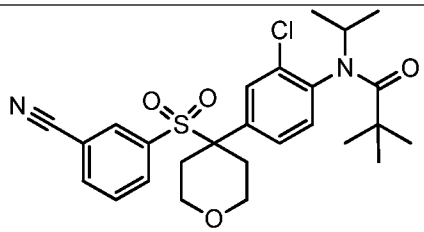
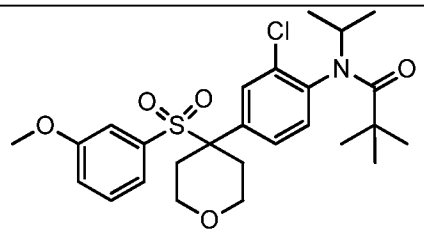
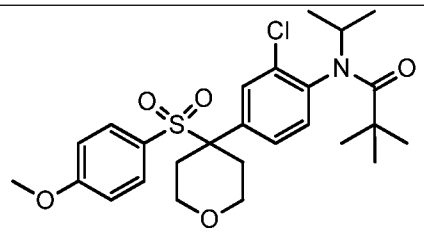
Ex #	Structure
102	 *N*-(5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide
103	 *N*-(2-chloro-4-(4-((3-chloro-4-methylphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
104	 *N*-(2-chloro-4-(3-((4-chlorophenyl)sulfonyl)bicyclo[3.1.0]hexan-3-yl)phenyl)-*N*-isopropylpivalamide
105	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-(cyclopropylmethyl)pivalamide
106	 *N*-(2-chloro-4-(4-((3-chloro-4-fluorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

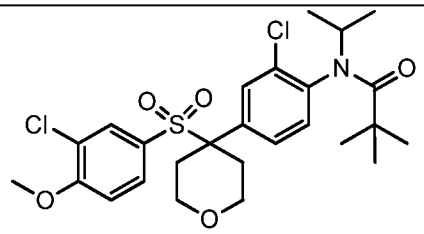
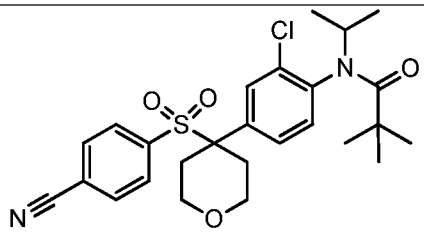
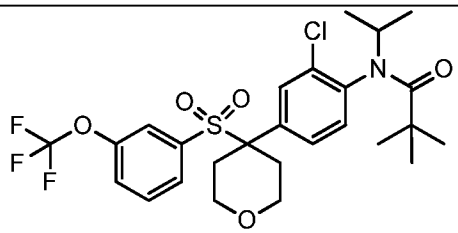
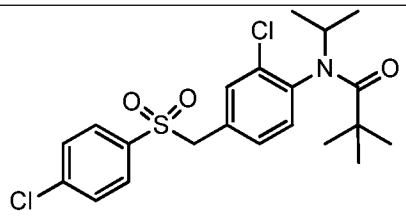
Ex #	Structure
107	 *N*-(2-chloro-4-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)-*N*-isopropylpivalamide
108	 *N*-(2-chloro-4-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
109	 *N*-(2-chloro-4-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)phenyl)-*N*-isopropylpivalamide
110	 *N*-(5-(((4-chlorophenyl)sulfonyl)methyl)-4,6-dimethylpyrimidin-2-yl)-*N*-ethylpivalamide
111	 *N*-isopropyl-*N*-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)pivalamide

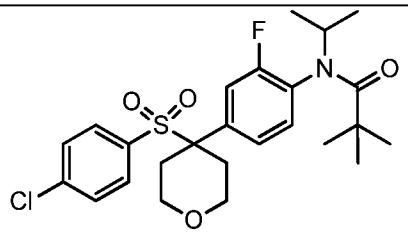
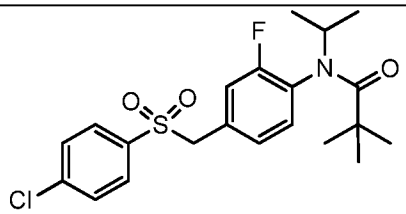
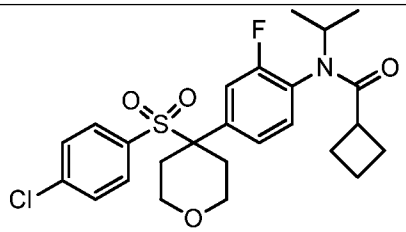
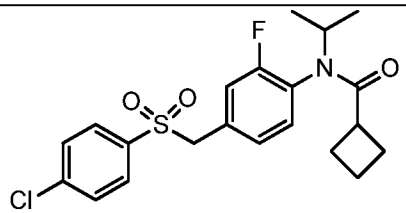
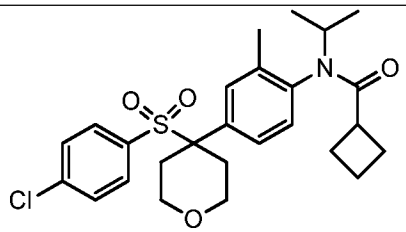
Ex #	Structure
112	 *N*-ethyl-*N*-(5-(5-((3-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)pivalamide
113	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-cyclobutylpivalamide
114	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-isopropylpivalamide
115	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclopropylpivalamide

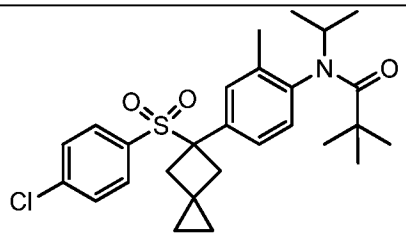
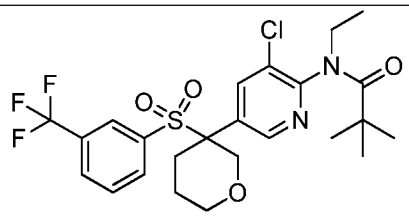
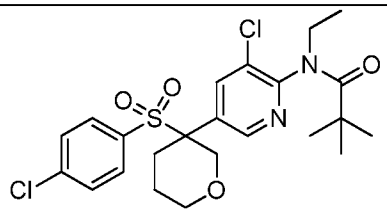
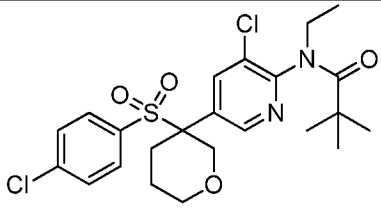
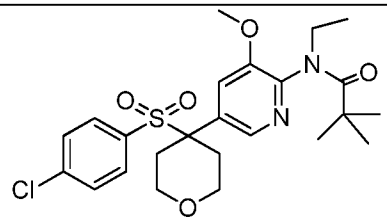
Ex #	Structure
116	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylpivalamide
117	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylcyclobutanecarboxamide
118	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclopentylpivalamide
119	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-(cyclopropylmethyl)pivalamide

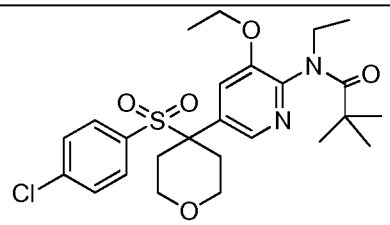
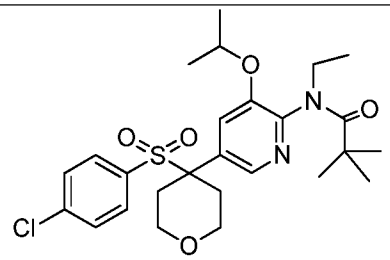
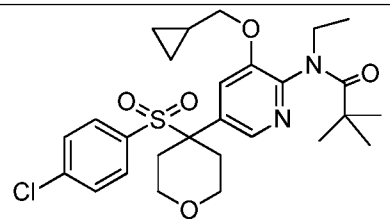
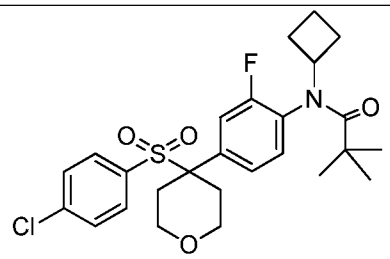
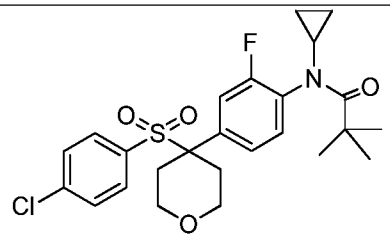
Ex #	Structure
120	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-cyclopentylpivalamide
121	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-cyclobutylpivalamide
122	 *N*-(2-chloro-4-(4-((3-fluorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
123	 *N*-(2-chloro-4-(4-((4-(trifluoromethoxy)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
124	 *N*-(2-chloro-4-(4-((3,4-dichlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

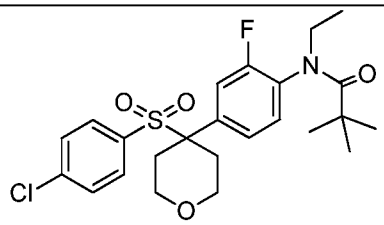
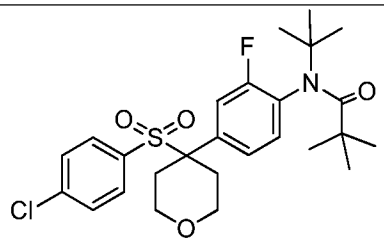
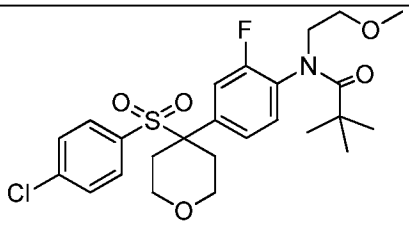
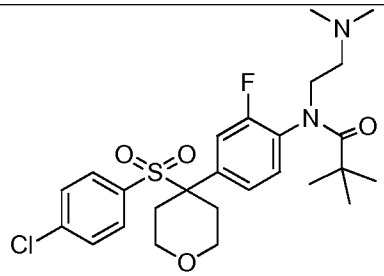
Ex #	Structure
125	 *N*-(2-chloro-4-(4-((3-fluoro-4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
126	 *N*-(2-chloro-4-(4-((3-cyanophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
127	 *N*-(2-chloro-4-(4-((3-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
128	 *N*-(2-chloro-4-(4-((4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

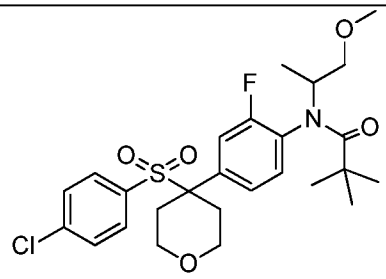
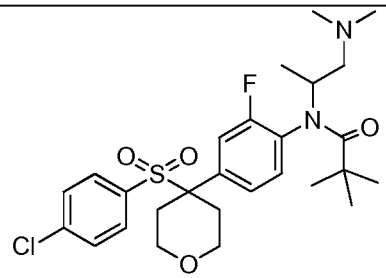
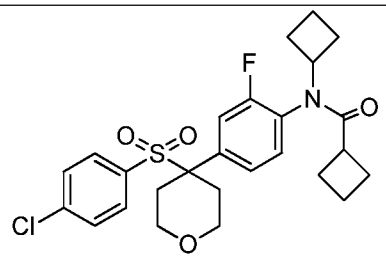
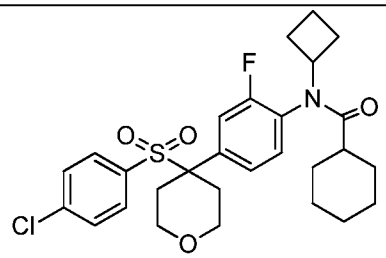
Ex #	Structure
129	 *N*-(2-chloro-4-(4-((3-chloro-4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
130	 *N*-(2-chloro-4-(4-((4-cyanophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
131	 *N*-(2-chloro-4-(4-((3-(trifluoromethoxy)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
132	 *N*-(2-chloro-4-(((4-chlorophenyl)sulfonyl)methyl)phenyl)-*N*-isopropylpivalamide

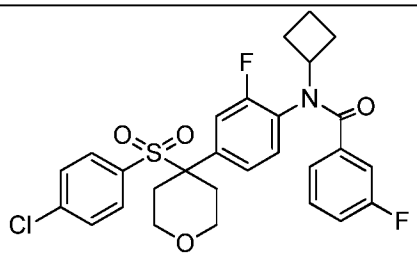
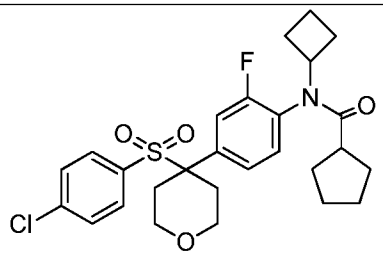
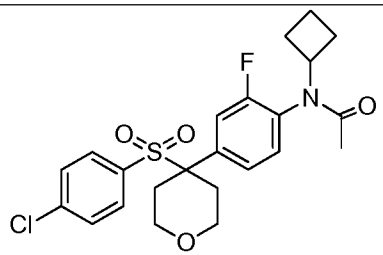
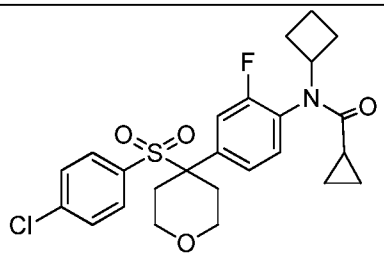
Ex #	Structure
133	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpivalamide
134	 *N*-(4-(((4-chlorophenyl)sulfonyl)methyl)-2-fluorophenyl)-*N*-isopropylpivalamide
135	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylcyclobutanecarboxamide
136	 *N*-(4-(((4-chlorophenyl)sulfonyl)methyl)-2-fluorophenyl)-*N*-isopropylcyclobutanecarboxamide
137	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-isopropylcyclobutanecarboxamide

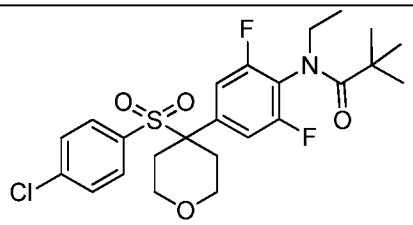
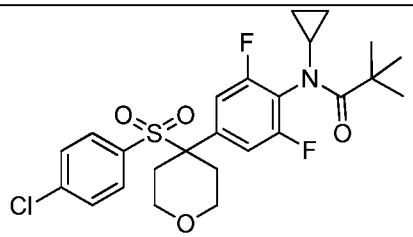
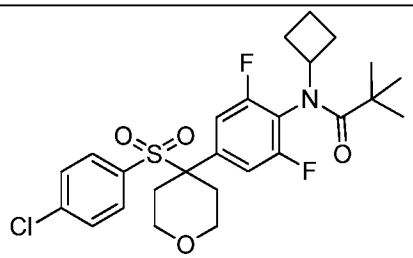
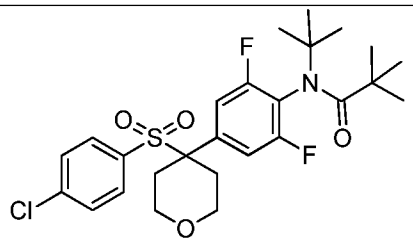
Ex #	Structure
138	 *N*-(4-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-2-methylphenyl)-*N*-isopropylpivalamide
139	 *N*-(3-chloro-5-(3-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide
140	 *N*-(3-chloro-5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide enantiomer 1
141	 *N*-(3-chloro-5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide enantiomer 2
148	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methoxypyridin-2-yl)-*N*-ethylpivalamide

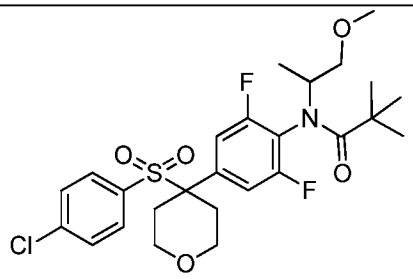
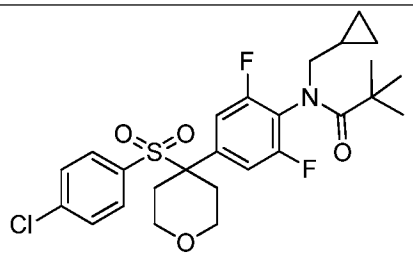
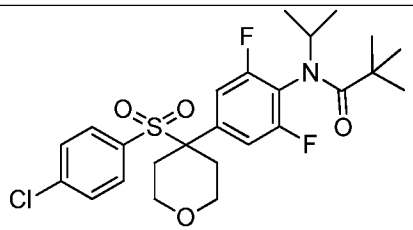
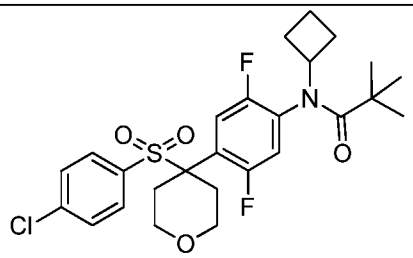
Ex #	Structure
149	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-ethoxypyridin-2-yl)-*N*-ethylpivalamide
150	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-isopropoxypyridin-2-yl)-*N*-ethylpivalamide
151	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-(cyclopropylmethoxy)pyridin-2-yl)-*N*-ethylpivalamide
152	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylpivalamide
153	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclopropylpivalamide

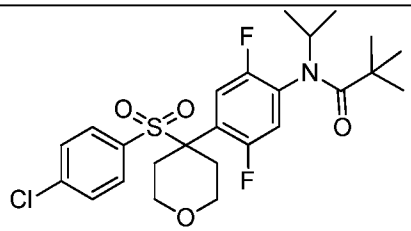
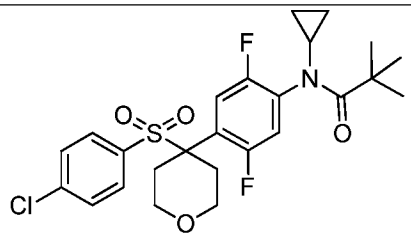
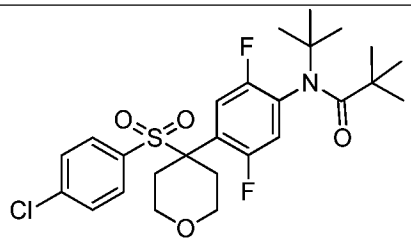
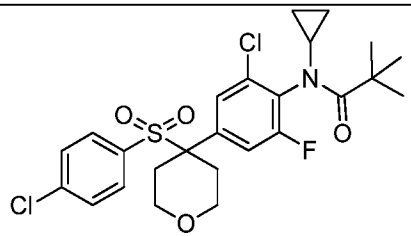
Ex #	Structure
154	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-ethylpivalamide
155	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)pivalamide
156	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-methoxyethyl)pivalamide
157	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-(dimethylamino)ethyl)pivalamide

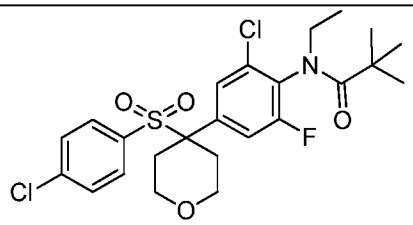
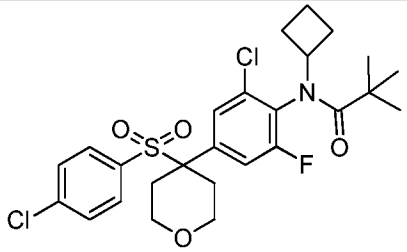
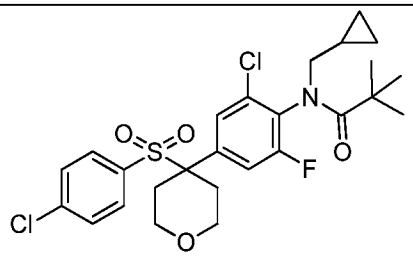
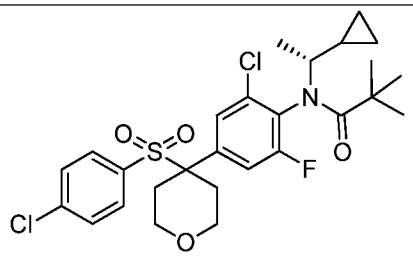
Ex #	Structure
158	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-methoxypropan-2-yl)pivalamide
159	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-(dimethylamino)propan-2-yl)pivalamide
160	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclobutanecarboxamide
161	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclohexanecarboxamide

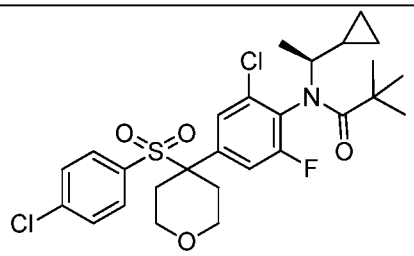
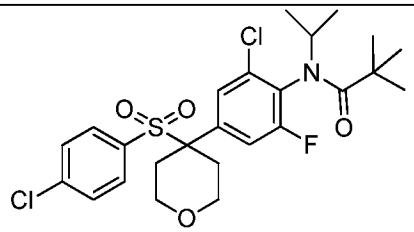
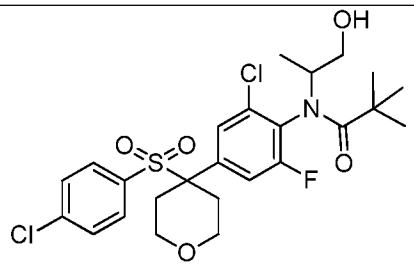
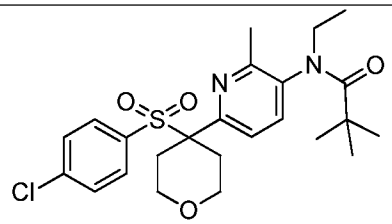
Ex #	Structure
162	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutyl-3-fluorobenzamide
163	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclopentanecarboxamide
164	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylacetamide
165	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclopropanecarboxamide

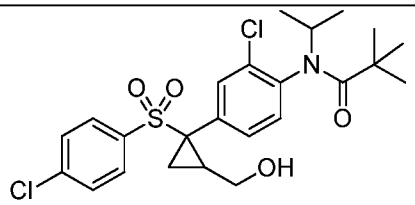
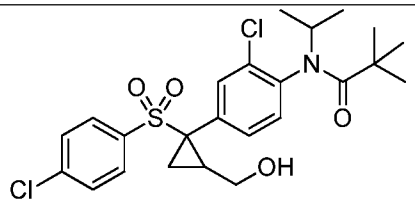
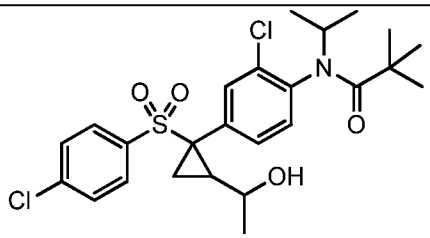
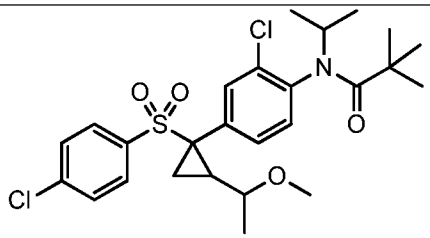
Ex #	Structure
166	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-ethylpivalamide
167	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-cyclopropylpivalamide
168	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-cyclobutylpivalamide
169	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)pivalamide

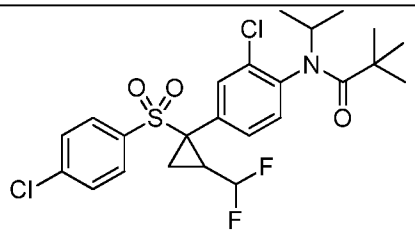
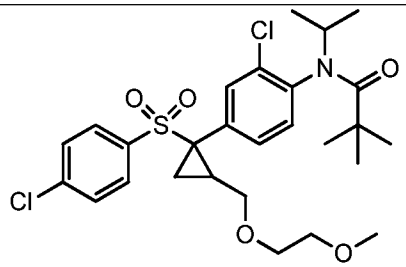
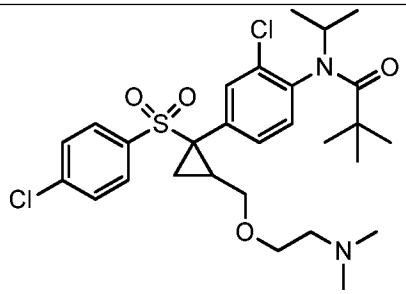
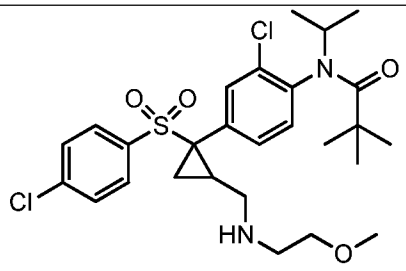
Ex #	Structure
170	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-(1-methoxypropan-2-yl)pivalamide
171	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-(cyclopropylmethyl)pivalamide
172	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-isopropylpivalamide
173	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-cyclobutylpivalamide

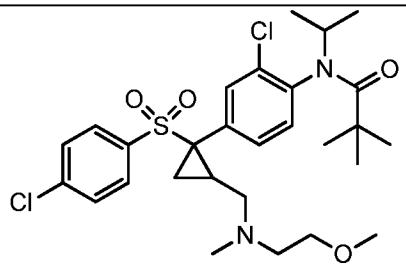
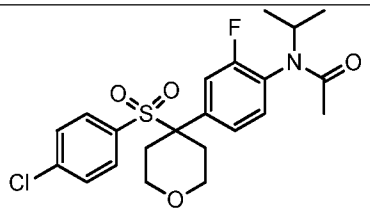
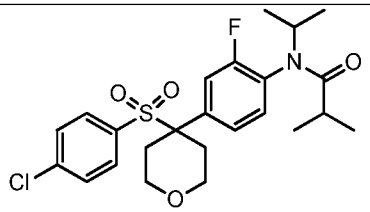
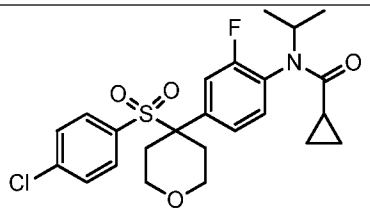
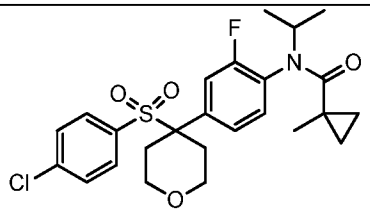
Ex #	Structure
174	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-isopropylpivalamide
175	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-cyclopropylpivalamide
176	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)pivalamide
177	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-cyclopropylpivalamide

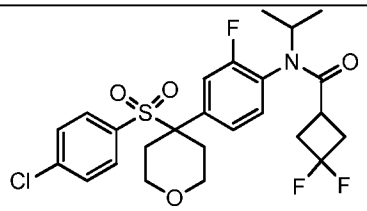
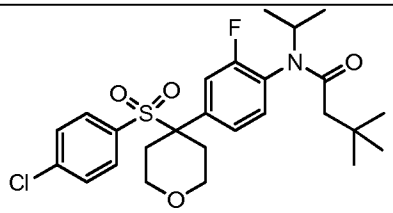
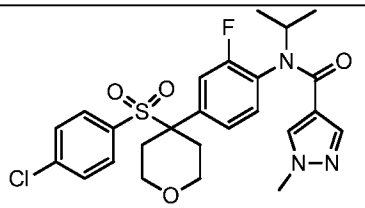
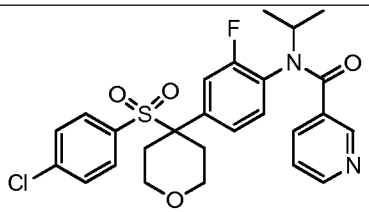
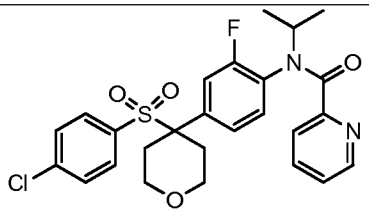
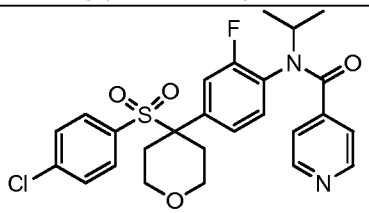
Ex #	Structure
178	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-ethylpivalamide
179	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-cyclobutylpivalamide
180	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(cyclopropylmethyl)pivalamide
181	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide

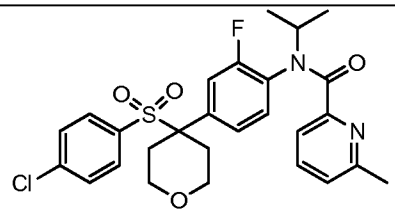
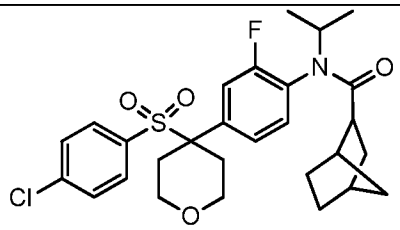
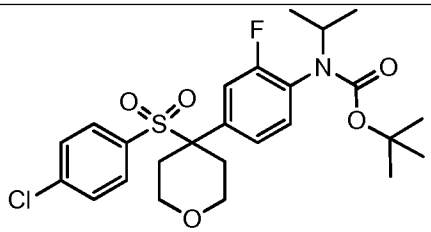
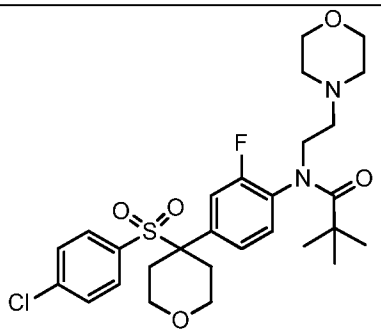
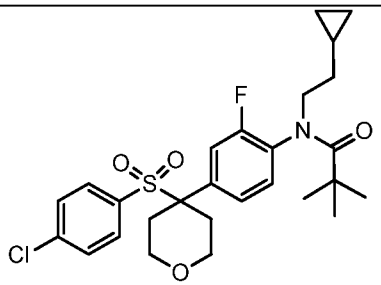
Ex #	Structure
182	 (*S*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide
183	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-isopropylpivalamide
184	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-hydroxypropan-2-yl)pivalamide
185	 *N*-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylpyridin-3-yl)-*N*-ethylpivalamide

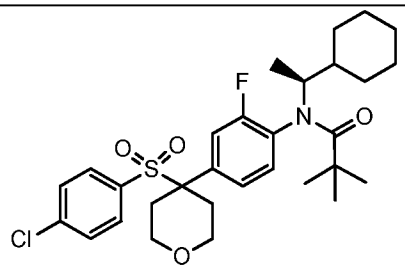
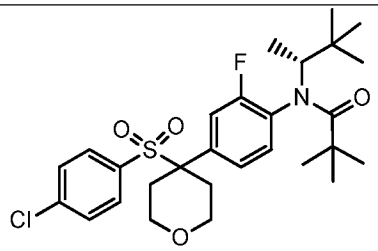
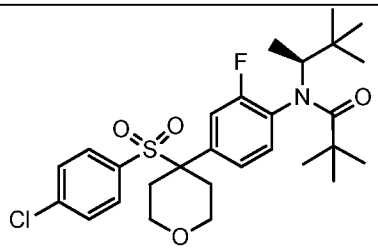
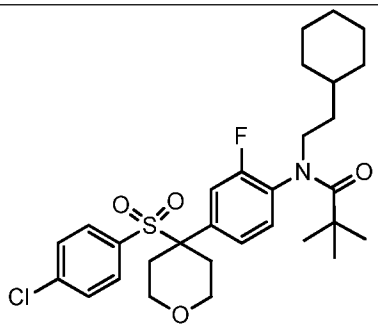
Ex #	Structure
187	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(hydroxymethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide isomer 1
188	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(hydroxymethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide isomer 2
189	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(1-hydroxyethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
190	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(1-methoxyethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide

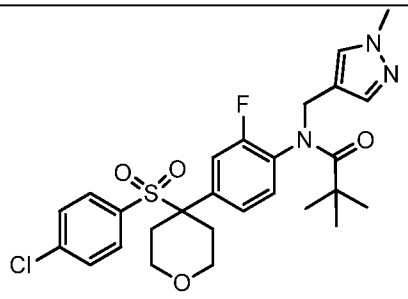
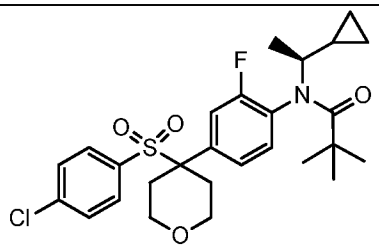
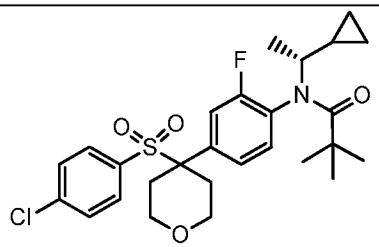
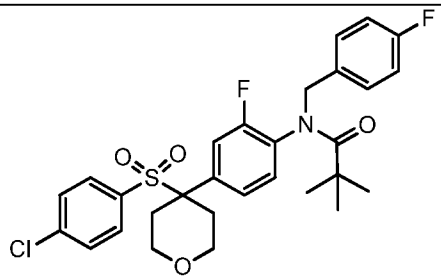
Ex #	Structure
191	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(difluoromethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
192	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-((2-methoxyethoxy)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
193	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-((2-(dimethylamino)ethoxy)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
194	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(((2-methoxyethyl)amino)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide

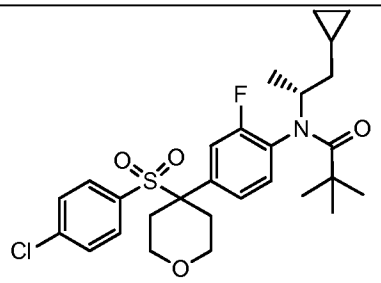
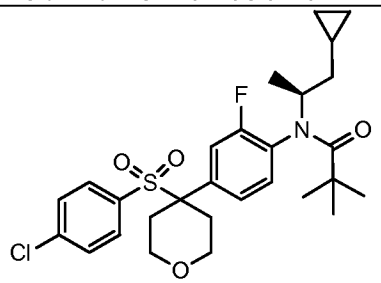
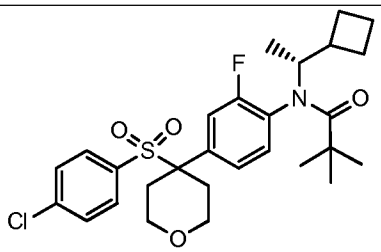
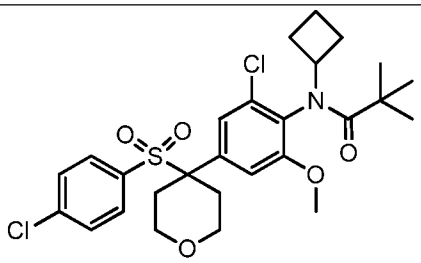
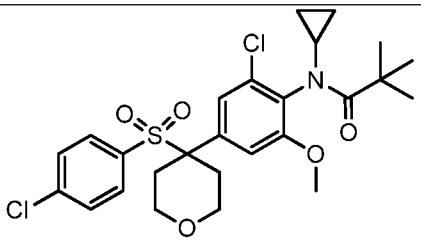
Ex #	Structure
195	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(((2-methoxyethyl)(methyl)amino)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
196	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylacetamide
197	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylisobutyramide
198	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylcyclopropanecarboxamide
199	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-1-methylcyclopropanecarboxamide

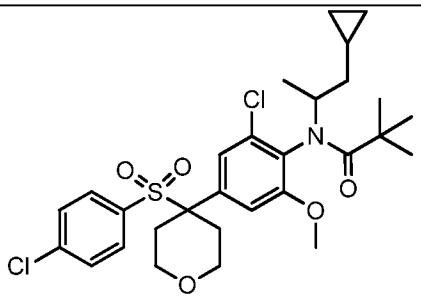
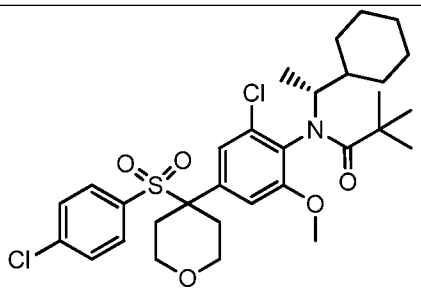
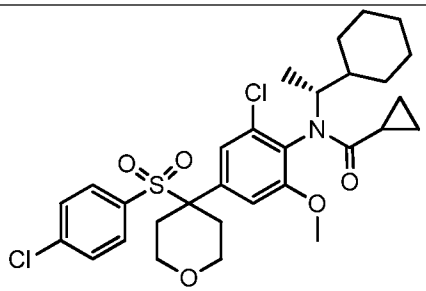
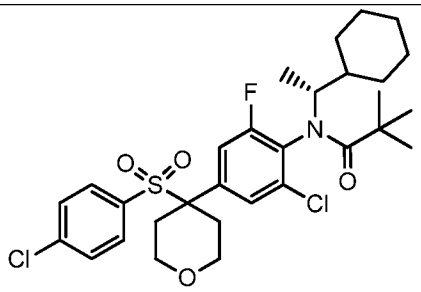
Ex #	Structure
200	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-3,3-difluoro-*N*-isopropylcyclobutanecarboxamide
201	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-3,3-dimethylbutanamide
202	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-1-methyl-1*H*-pyrazole-4-carboxamide
203	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylnicotinamide
204	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpicolinamide
205	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylisonicotinamide

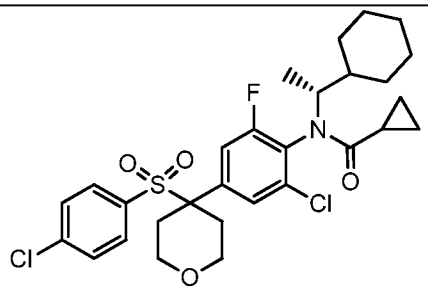
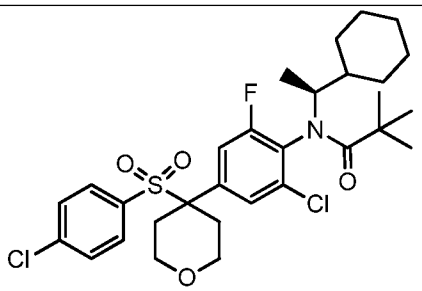
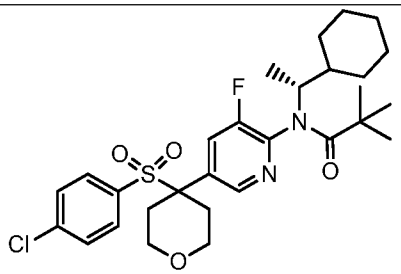
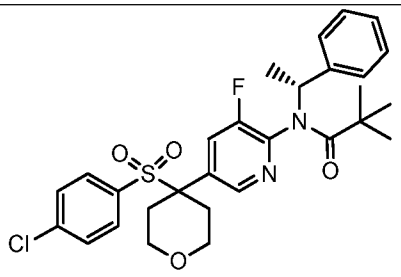
Ex #	Structure
206	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-6-methylpicolinamide
207	 (1*R*,4*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylbicyclo[2.2.1]heptane-2-carboxamide
208	 *tert*-butyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate
209	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-morpholinoethyl)pivalamide
210	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-cyclopropylethyl)pivalamide

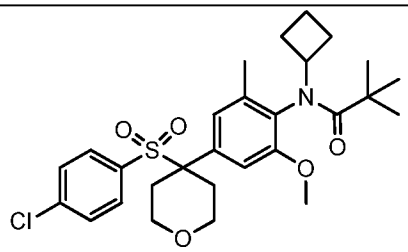
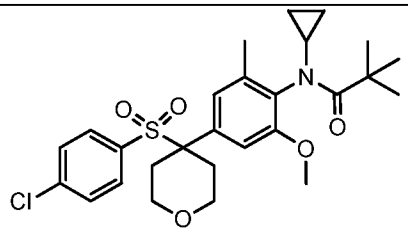
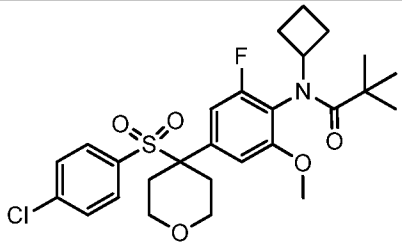
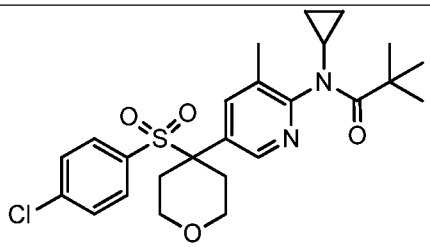
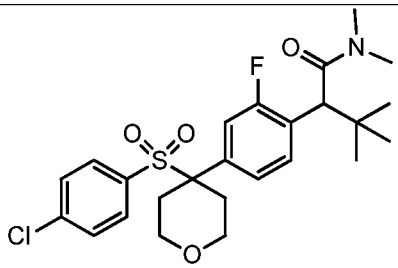
Ex #	Structure
211	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide
212	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(3,3-dimethylbutan-2-yl)pivalamide
213	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(3,3-dimethylbutan-2-yl)pivalamide
214	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-cyclohexylethyl)pivalamide

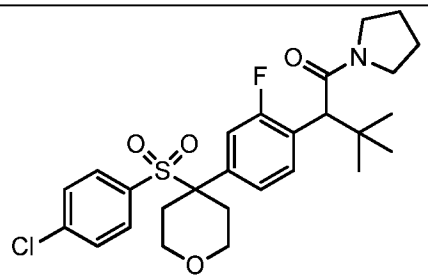
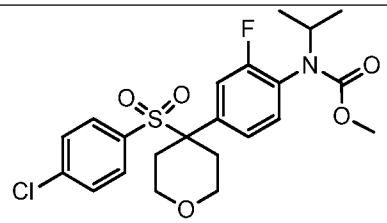
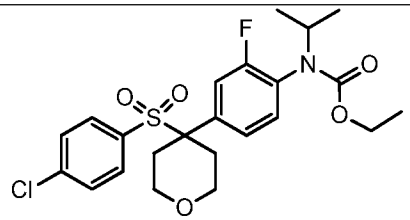
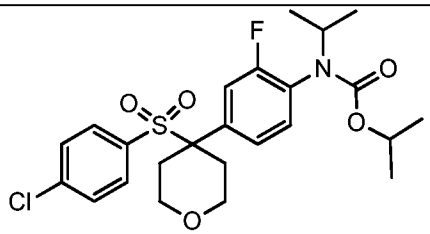
Ex #	Structure
215	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl)pivalamide
216	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide
217	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide
218	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(4-fluorobenzyl)pivalamide

Ex #	Structure
219	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
220	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
221	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclobutylethyl)pivalamide
222	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-cyclobutylpivalamide
223	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-cyclopropylpivalamide

Ex #	Structure
224	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
225	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclohexylethyl)pivalamide
226	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclohexylethyl)cyclopropanecarboxamide
227	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide

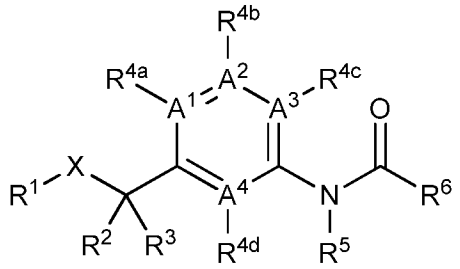
Ex #	Structure
228	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)cyclopropanecarboxamide
229	 (*S*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide
230	 (*R*)-*N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-(1-cyclohexylethyl)pivalamide
231	 (*R*)-*N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-(1-phenylethyl)pivalamide

Ex #	Structure
232	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methoxy-6-methylphenyl)-*N*-cyclobutylpivalamide
233	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methoxy-6-methylphenyl)-*N*-cyclopropylpivalamide
234	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluoro-6-methoxyphenyl)-*N*-cyclobutylpivalamide
235	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-cyclopropylpivalamide
236	 2-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*,*N*,3,3-tetramethylbutanamide

Ex #	Structure
237	 2-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one
238	 methyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate
239	 ethyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate
240	 isopropyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

, or pharmaceutically acceptable salts thereof.

[00228] In another aspect, the invention provides aryl sulfones and related compounds that are modulators of ROR-gamma activity, wherein the modulators are compounds of Formula Ib:



Formula Ib

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

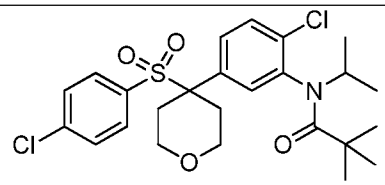
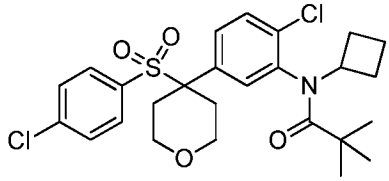
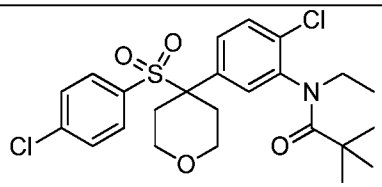
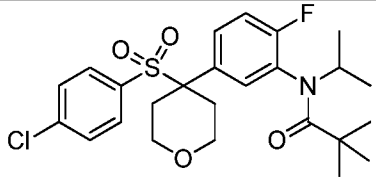
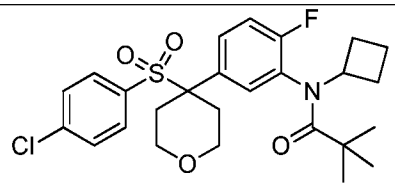
R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

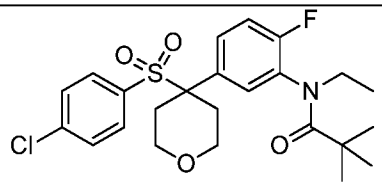
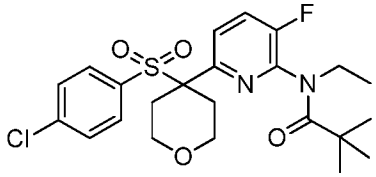
R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or

R^{4c} and R^6 taken together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

[00229] For example, the compound of Formula Ib can be a compound as shown in Table 2.

Table 2. Exemplary Embodiments of the Compounds of Formula Ib.

Ex #	Structure
142	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
143	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylpivalamide
144	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-ethylpivalamide
145	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpivalamide
146	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylpivalamide

Ex #	Structure
147	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-ethylpivalamide
186	 *N*-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-ethylpivalamide

or a pharmaceutically acceptable salt thereof.

Formulations, Administrations, and Uses

[00230] In another aspect, the invention includes a pharmaceutical composition comprising a compound of Formula I, Formula Ia, Formula Ia[1], or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or adjuvant. In some embodiments of this aspect, the invention includes pharmaceutically acceptable salts of the compounds of Tables 1 and 2.

[00231] The present invention includes within its scope pharmaceutically acceptable prodrugs of the compounds of the present invention. A "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. In some embodiments, the prodrugs increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal or which enhance delivery of the parent compound to a biological compartment relative to the parent species.

[00232] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate,

partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00233] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[00234] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00235] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable

diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00236] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00237] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00238] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00239] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00240] Topical application for the lower intestinal tract can be effected in a rectal

suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00241] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00242] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00243] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00244] In some exemplary embodiments, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[00245] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated and the particular mode of administration. In some embodiments, the compositions should be formulated so that a dosage of between about 0.01 to about 100 mg/kg body weight/day of the modulator can be administered to a patient receiving these compositions.

[00246] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific

compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[00247] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

Methods

[00248] The compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, can inhibit the activity of an ROR-gamma receptor. For example, the compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, can inhibit the activity of an ROR-gamma receptor *in vitro*. The compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, can also inhibit the activity of an ROR-gamma receptor *in vivo*.

[00249] In one aspect, thus, the invention includes a method of inhibiting the activity of an ROR-gamma receptor, comprising contacting the receptor with a compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof. In one embodiment of this aspect, the compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, inhibits the activity of an ROR-gamma receptor *in vitro*. In another embodiment, the compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, inhibits the activity of an ROR-gamma receptor *in vivo*. In some embodiments, the compound of Formula I is a modulator of ROR-gamma activity. In some embodiments, the compound of Formula Ia is a modulator of ROR-gamma activity. In some embodiments, the compound of Formula Ia^1 is a modulator of ROR-gamma activity. In some embodiments, the compound of Formula Ib is a modulator of ROR-gamma activity.

[00250] In another aspect, the invention includes a method of treating or reducing the severity of an ROR-gamma receptor mediated disease in a patient comprising administering a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

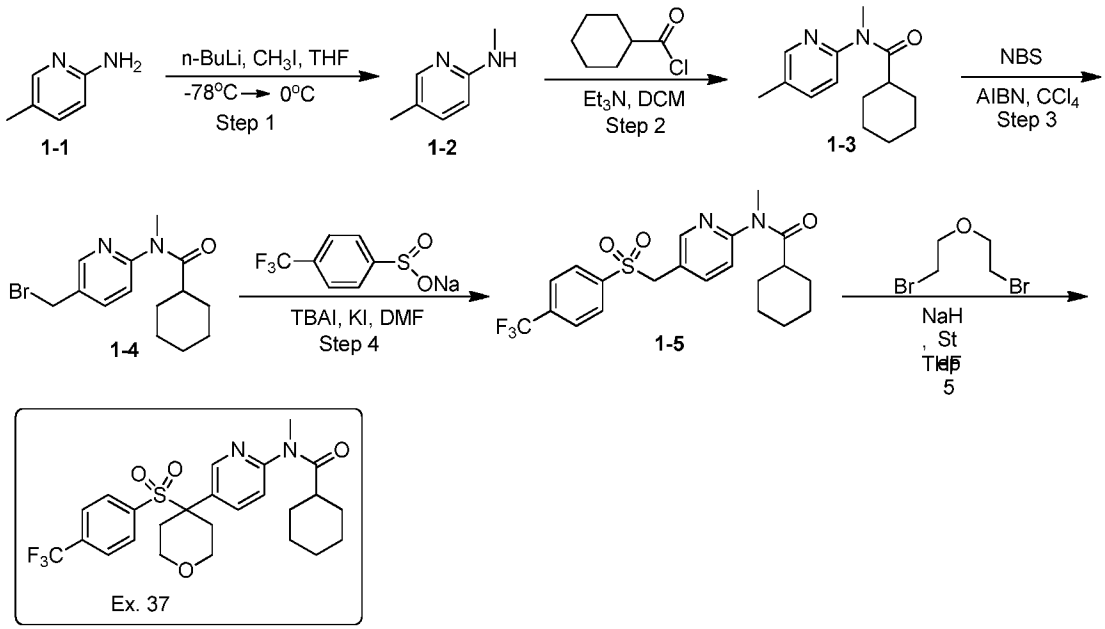
[00251] In some embodiments of this aspect, an ROR-gamma receptor mediated disease can include an automimmune disease. In some embodiments, an autoimmune disease is selected from the group consisting of Ankylosing, spondylitis, Asthma, Behcet's disease, Chronic obstructive pulmonary disease, Crohn's disease, Diabetes Mellitus Type 1, Multiple Sclerosis, Neuromyelitis optica, Polymyalgia Rheumatica, Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, Scleroderma, Sjögren's syndrome, Systemic Lupus Erythematosus, Systemic sclerosis, Transplant rejection, Inflammatory Bowel Disease, Ulcerative Colitis and Uveitis.

[00252] In another aspect, the invention includes a method of modulating the activity of an ROR-gamma receptor with a modulator of ROR-gamma, comprising contacting the receptor with a compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof. In one embodiment of this aspect, the compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, modulates the activity of an ROR-gamma receptor *in vitro*. In another embodiment, the compound of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, modulates the activity of an ROR-gamma receptor *in vivo*. In one embodiment, the compound of Formula I is a modulator of the ROR-gamma receptor. In one embodiment, the compound of Formula Ia is a modulator of the ROR-gamma receptor. In one embodiment, the compound of Formula Ia^1 is a modulator of the ROR-gamma receptor In one embodiment, the compound of Formula Ib is a modulator of the ROR-gamma receptor.

Synthetic Procedures

[00253] The compounds of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, may be readily synthesized from commercially available starting materials using methods known in the art. Exemplary synthetic routes to produce compounds of Formula I, Formula Ia, Formula Ia^1, or Formula Ib, or a pharmaceutically acceptable salt thereof, are provided in the general schemes and examples below. The examples below are given to provide a better understanding of the synthetic procedures of the invention and are not meant to be limiting in any way.

[00254] Scheme 1. Synthesis of Example #37



[00255] Step 1: n-BuLi (12 mL, 30.6 mmol) was added to a solution of compound **1-1** (3.0 g, 27.8 mmol) in THF (60 mL) at -78 °C. The mixture was stirred for 0.5h at 0 °C. Then, CH_3I (4.3 g, 30.6 mmol) was added. The reaction mixture was stirred for another 2 hours at room temperature. Water (60 mL) was added. The mixture was extracted with EtOAc (50 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (PE/EA=2/1) to give the desired product **1-1** as yellow oil. LC-MS: m/z = 123.2 $[M+H]^+$.

[00256] Step 2: Cyclohexanecarbonyl chloride (1.5 g, 10.1 mmol) was added to a solution of compound **1-2** (0.5 g, 4.6 mmol) and Et_3N (1.4 g, 13.8 mmol) in DCM (20 mL). The mixture was stirred for 0.5 hour at room temperature. Water (20 mL) was added. The mixture was extracted with DCM (15 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the desired product **1-3** as yellow solid. LC-MS: m/z = 233.2 $[M+H]^+$.

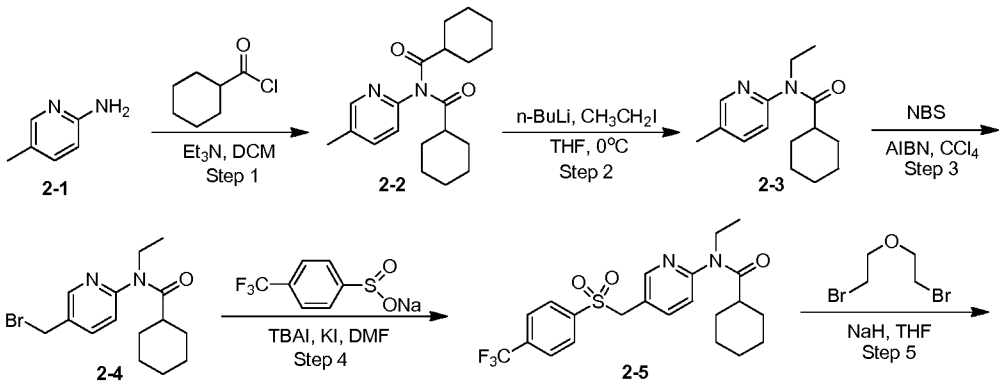
[00257] Step 3: Compound **1-3** (2.7 g, 11.6 mmol), NBS (4.1 g, 23.2 mmol) and AIBN (1.9 g, 11.6 mmol) in CCl_4 (50 mL) was stirred for overnight at 70 °C. The mixture was filtered, and the filtrate was added to water (60 mL). The mixture was extracted with DCM (40 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude product **1-4** as yellow oil. LC-MS: m/z = 311.1 $[M+H]^+$.

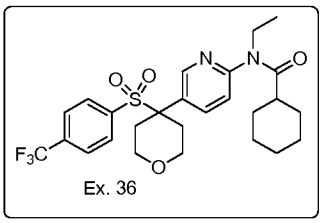
[00258] Step 4: Sodium 4-(trifluoromethyl)benzenesulfinate (0.34 g, 1.46 mmol), compound **1-4** (0.3 g, 0.97 mmol), TBAI (0.36 g, 0.97 mmol) and KI (0.24 g, 1.46 mmol) in DMF (50

mL) was stirred for overnight at 30 °C. Water (20 mL) was added. The mixture was extracted with EtOAc (20 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=2/1) to give the product **1-5** as white solid. LC-MS: m/z = 441.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 - 7.31 (m, 7H), 4.32 (s, 2H), 3.42 - 3.16 (s, 3H), 2.49 - 2.45 (m, 1H), 1.85 - 0.97 (m, 10H).

[00259] Example #37:. NaH (8 mg, 1.15 mmol) was added to a solution of compound **1-5** (100 mg, 0.23 mmol) in THF (10 mL). Then 1-bromo-2-(2-bromoethoxy)ethane (107 mg, 0.46 mmol) was added and stirred overnight at 50 °C. The mixture was cooled to room temperature. Water (10 mL) was added. The mixture was extracted with DCM (15 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by pre-TLC and pre-HPLC to give the desired product as white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.68 - 7.58 (m, 6H), 4.02 - 3.99 (m, 2H), 3.46 (s, 3H), 3.33 - 3.31 (m, 2H), 2.60 - 2.41 (m, 5H), 1.82 - 1.62 (m, 8H), 1.25 - 1.23 (m, 2H); HPLC = 99.5% (214 nm), 100% (254 nm), t_R = 4.72 min. LC-MS: m/z = 511.1 $[M+H]^+$, t_R = 1.64 min.

[00260] Scheme 2. Synthesis of Example #36





[00261] Step 1: Cyclohexanecarbonyl chloride (5.4 g, 37 mmol) was added to a solution of 5-methylpyridin-2-amine **2-1** (2.0 g, 18.5 mmol) and Et_3N (5.6 g, 55.5 mmol) in DCM (40 mL). The mixture was stirred for 3 hours at room temperature. Water (50 mL) was added. The mixture was extracted with DCM (40 mL x 2). Combined organic layer was washed with

brine, dried over anhydrous Na_2SO_4 and concentrated to give the product **2-2** as yellow solid. LC-MS: m/z = 329.3 $[M+H]^+$.

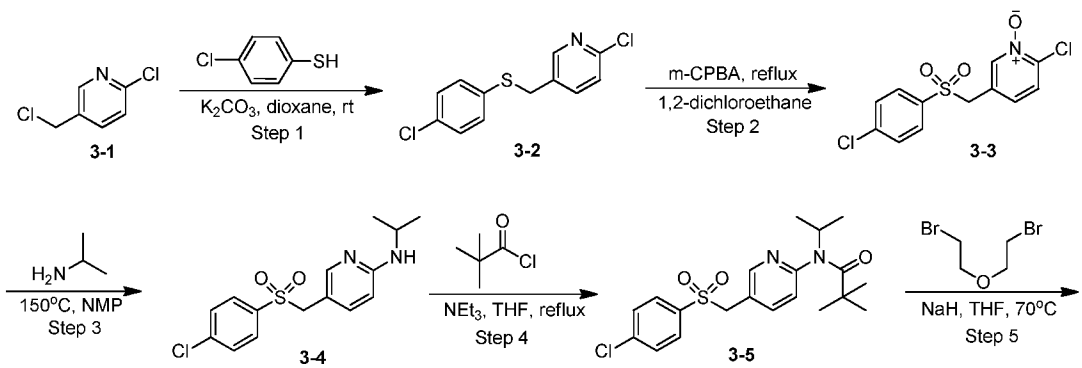
[00262] **Step 2**: n-BuLi (9.1 mL, 22.8 mmol) was added dropwise to a solution of compound **2-2** (3.0 g, 9.1 mmol) in THF (50 mL) at 0 °C. The mixture was stirred for 1h at 0 °C. CH_3CH_2I (1.7 g, 10.9 mmol) was added. The reaction mixture was stirred for another 2 hours at room temperature. Then the mixture was stirred overnight at 70 °C. The solvent was removed by reduced pressure. The residue was purified by silica-gel column chromatography (PE/EA=2/1) to give the desired product **2-3** as yellow oil. LC-MS: m/z = 247.2 $[M+H]^+$.

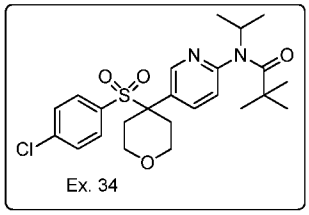
[00263] **Step 3**: The same procedure with the **step 3** of **Scheme 1** was applied to the preparation of compound **2-4**. LC-MS: m/z = 325.1 $[M+H]^+$.

[00264] **Step 4**: The same procedure with the **step 4** of **Scheme 1** was applied to the preparation of compound **2-5**. LC-MS: m/z = 455.1 $[M+H]^+$.

[00265] **Example #36**: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of **Example #36**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.68 - 7.58 (m, 6H), 4.02 - 3.88 (m, 4H), 3.35 - 3.28 (m, 2H), 2.65 - 2.39 (m, 5H), 194 - 1.50 (m, 7H), 1.24 - 1.10 (m, 6H). HPLC = 99.8% (214 nm), 100% (254 nm), t_R = 4.84 min. LC-MS: m/z = 525.2 $[M+H]^+$, t_R = 1.68 min.

[00266] **Scheme 3. Synthesis of Examples #21 and 34**





[00267] **Step 1**: 4-chlorobenzenethiol (1.339 g, 9.3 mmol), compound **3-1** (1 g, 6.17 mmol), K_2CO_3 (2.567 g, 18.6 mmol) in dioxane (20 mL) was stirred for 1.5 hrs at 30 °C. After

filtered, the filtrate was concentrated. Water (20 mL) was added to the resulting residue. The mixture was extracted with EtOAc (20 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=20/1) to give the product **3-2** as white solid. LC-MS: m/z = 269.9 $[M+H]^+$.

[00268] **Step 2**: To a solution of compound **3-2** (7.6 g, 25 mmol) in 1,2-dichloroethane (100 mL) was added m-CPBA (13 g, 75 mmol) at rt. The reaction mixture was refluxed overnight, then diluted with EtOAc (10 mL), washed with saturated $Na_2S_2O_3$ (100 mL), 4N NaOH (100 mL), brine(100 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography eluting with PE/EA = 1/1 to give target compound **3-3** as yellow solid. LC-MS: m/z = 317.9 $[M+H]^+$.

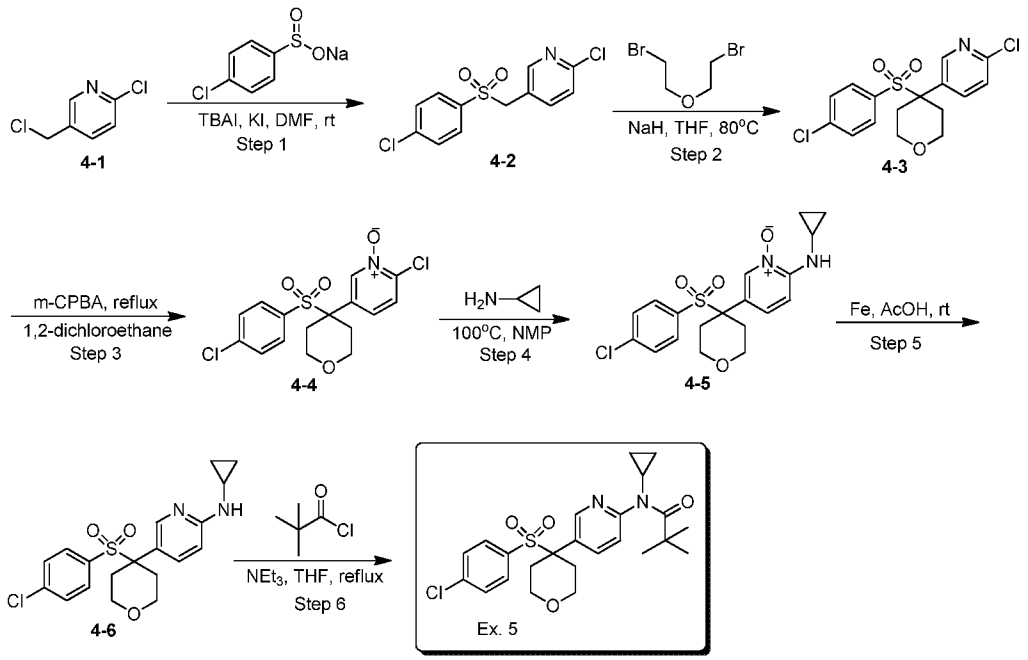
[00269] **Step 3**: A mixture of compound **3-3** (0.7 g, 2.2 mmol), TEA (0.667 g, 6.6 mmol), propan-2-amine (0.39 g, 6.6 mmol) in NMP (5 mL) was stirred at 150 °C for 15 hrs. After concentrated, the crude product was purified by column chromatography eluting with DCM/MeOH = 20/1 to give target compound **3-4** as yellow oil. LC-MS: m/z = 325.0 $[M+H]^+$.

[00270] **Step 4**: A mixture of compound **3-4** (0.21 g, 0.65 mmol), TEA (0.263 g, 2.6 mmol), pivaloyl chloride (0.234 g, 1.94 mmol) in THF (15 mL) was refluxed for 24 hrs. After being washed with brine (100 mL), the mixture was dried over anhydrous Na_2SO_4, and concentrated to the residue. The residue was purified by column chromatography eluting with PE/EA = 3/1 to give target compound **3-5** as yellow solid. LC-MS: m/z = 409.1 $[M+H]^+$.

[00271] **Example #34**: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of compound **Example #34**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.78 - 7.75 (m, 1H), 7.37 - 7.29 (m, 4H), 7.20 - 7.17 (m, 1H), 5.00 - 4.75 (m, 1H), 4.02 (d, *J* = 11.1 Hz, 2H), 3.26 (t, *J* = 11.4 Hz, 2H), 2.66 (t, *J* = 10.8 Hz, 2H), 2.40 (d, *J* = 14.1 Hz, 2H), 1.45 - 0.84 (m, 15H). HPLC = 98.7% (214 nm), 100% (254 nm), t_R = 4.39 min. LC-MS: m/z = 479.0 $[M+H]^+$.

[00272] **Example #21:** was prepared following the procedure for **Example** 34, but 2-methylpropane-2-amine in **step 3** and cyclobutanecarbonyl chloride in **step 4**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.91 - 7.65 (m, 1H), 7.39 - 7.31 (m, 4H), 7.13 (d, *J* = 8.1 Hz, 1H), 4.05 (d, *J* = 10.2 Hz, 2H), 3.28 (t, *J* = 11.4 Hz, 2H), 2.79 - 2.56 (m, 3H), 2.51 - 2.22 (m, 4H), 1.77 - 1.56 (m, 4H), 1.32 (s, 9H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.45 min. LC-MS: m/z = 491.0 $[M+H]^+$.

[00273] Scheme 4. Synthesis of Examples #5, 10, 11, 12, 13, 14, 17, 19, 22, 23, 25, 26, 27, 30, 102, and 111.



[00274] Step 1: sodium 4-chlorobenzenesulfinate (1 g, 6.17 mmol), compound **4-1** (1.56 g, 7.4 mmol), Bu_4NI (1.37 g, 3.7 mmol), KI (0.615 g, 3.7 mmol) in DMF (30 mL) was stirred at 30 °C for 1 hrs. After being filtered, the filtrate was concentrated. Water (100 mL) was added to the resulting residue. The mixture was extracted with EtOAc (50 mL x 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=10/1) to give the product **4-2** as yellow solid. LC-MS: m/z = 301.9 $[M+H]^+$.

[00275] Step 2: To a solution of compound **4-2** (6.6 g, 21.8 mmol) in THF (120 mL) was added NaH (70%w/w 1.5 g, 43.7 mmol) in portions. After the mixture stirred at room temperature for 10 min, 1-bromo-2-(2-bromoethoxy)ethane (10 g, 43.7 mmol) was added and the resulting mixture was refluxed for 4 hrs. Brine (100 mL) was added. The mixture was extracted with EtOAc (50 mL x 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (DCM/MeOH = 30/1) to give the product **4-3** as yellow solid. LC-MS: m/z = 371.9 $[M+H]^+$.

[00276] Step 3: To a solution of compound **4-3** (2 g, 5.38 mmol) in 1,2-dichloroethane (50 mL) was added m-CPBA (2.79 g, 16.1 mmol) at rt. The reaction mixture was refluxed overnight, then diluted with EtOAc (10 mL), washed with saturated $Na_2S_2O_3$ (50 mL), 4N

NaOH (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative column chromatography eluting with DCM/MeOH = 20/1 to give target compound **4-4** as white solid. LC-MS: m/z = 387.9 $[M+H]^+$.

[00277] **Step 4**: A mixture of compound **4-4** (0.2 g, 0.52 mmol), cyclopropanamine (0.088 g, 1.55 mmol) in NMP (5 mL) was stirred at 100 °C for 48 hrs. After being concentrated to give the crude product, the crude product was purified by column chromatography eluting with DCM/MeOH = 25/1 to give target compound **4-5** as yellow oil, 0.107 g. LC-MS: m/z = 409.1 $[M+H]^+$.

[00278] **Step 5**: A mixture of compound **4-5** (0.107 g, 0.26 mmol), Iron powder (0.147 g, 2.62 mmol) in AcOH (20 mL) was stirred at r.t overnight. After being filtered, the filtrate was diluted with EA (60 mL) and 1 N NaOH (60 mL). The organic layer was washed with brine (60 mL), dried over anhydrous Na_2SO_4, and concentrated to the crude product. The crude product was purified by column chromatography eluting with DCM/MeOH = 25/1 to give target compound **4-6** as white solid.

[00279] **Example #25:** A mixture of compound **4-6** (0.08 g, 0.2 mmol), TEA (0.082 g, 0.82 mmol), pivaloyl chloride (0.074 g, 0.61 mmol) in THF (15 mL) was refluxed overnight. After being washed with brine (20 mL), the mixture was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by prep-TLC to give target compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 2.7 Hz, 1H), 7.74 (dd, J = 8.4, 2.7 Hz, 1H), 7.38 - 7.30 (m, 4H), 7.21 (d, J = 8.4 Hz, 1H), 4.01 (d, J = 11.4 Hz, 2H), 3.29 (t, J = 11.1 Hz, 2H), 3.03 - 2.92 (m, 1H), 2.79 - 2.59 (m, 2H), 2.39 (d, J = 13.2 Hz, 2H), 1.28 - 1.01 (m, 9H), 0.93 - 0.82 (m, 2H), 0.64 - 0.51 (m, 2H). HPLC = 98.5% (214 nm), 97.3% (254 nm), t_R = 4.25 min. LC-MS: m/z = 477.0 $[M+H]^+$.

[00280] **Example #26:** was prepared following the procedure for **Example 25**, but using cyclobutaneamine in **step 4**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.4, 2.7 Hz, 1H), 7.43 - 7.29 (m, 4H), 7.18 - 7.15 (m, 1H), 4.83 - 4.70 (m, 1H), 4.03 (d, J = 12.3 Hz, 2H), 3.28 (t, J = 11.4 Hz, 2H), 2.77 - 2.58 (m, 2H), 2.44 - 2.40 (m, 2H), 2.20 - 2.12 (m, 2H), 1.79 - 1.55 (m, 4H), 1.03 (s, 9H). HPLC = 97.1% (214 nm), 95.3% (254 nm), t_R = 4.48 min. LC-MS: m/z = 491.0 $[M+H]^+$.

[00281] **Example #30:** was prepared following the procedure for **Example 25**, but using 2-methoxyethaneamine in **step 4**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 - 7.72 (m, 1H), 7.47 - 7.27 (m, 5H), 4.02 - 3.88 (m, 4H), 3.57 (t, J = 5.4 Hz, 2H), 3.31 - 3.25 (m, 5H), 2.66 - 2.60 (m, 2H), 2.45 - 2.37 (m, 2H), 1.11 (s, 9H). HPLC = 99.4% (214 nm), 99.5% (254

nm), t_R = 4.20 min. LC-MS: m/z = 494.9 $[M+H]^+$.

[00282] Example #27: was prepared following the procedure for **Example 25**, but using ethaneamine in **step 4**: ^{1}H NMR (300 MHz, CDCl3) δ 8.15 (s, 1H), 7.80 - 7.77 (m,1H), 7.41 - 7.23 (m, 5H), 4.04 - 4.00 (m, 2H), 3.86 - 3.84 (m, 2H), 3.30 (t, J = 12.0 Hz, 2H), 2.77 - 2.52 (m, 2H), 2.43 - 2.39 (m,2H), 1.45 - 0.70 (m, 12H). HPLC = 99.7% (214 nm), 99.8% (254 nm), t_R = 4.23 min. LC-MS: m/z = 465.2 $[M+H]^+$.

[00283] Example #19: was prepared following the procedure for **Example 25**, but using cyclopropanemethaneamine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.4 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.41 - 7.35 (m, 4H), 7.29 (d, *J* = 6.9 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 2H), 3.66 (d, *J* = 6.9 Hz, 2H), 3.28 (t, *J* = 11.4 Hz, 2H), 2.80 - 2.59 (m, 2H), 2.42 (d, *J* = 12.9 Hz, 2H), 1.10 (s, 9H), 1.02 (s, 1H), 0.46 - 0.39 (m, 2H), 0.06 - 0.03 (m, 2H). HPLC = 98.8% (214 nm), 99.2% (254 nm), t_R = 4.57 min. LC-MS: m/z = 491.1 $[M+H]^+$.

[00284] Example #11: was prepared following the procedure for **Example 25**, but using oxybis(ethane-2,1)dimethanesulfonate in step 2 and ethaneamine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.4 Hz, 1H), 7.60 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.51 - 7.30 (m, 4H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 3.37 (d, *J* = 13.8 Hz, 2H), 2.73 (d, *J* = 13.8 Hz, 2H), 1.29 - 0.95 (m, 12H), 0.69 - 0.64 (m, 2H), 0.52 - 0.47 (m, 2H). HPLC = 95.2% (214 nm), 96.1% (254 nm), t_R = 5.03 min. LC-MS: m/z = 461.0 $[M+H]^+$.

[00285] Example #10: was prepared following the procedure for **Example 11** , but using propan-2-amine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.68 - 7.66 (m, 1H), 7.45 - 7.28 (m, 4H), 7.14 (d, *J* = 8.1 Hz, 1H), 4.93 - 4.78 (m, 1H), 3.38 (d, *J* = 13.2 Hz, 2H), 2.75 (d, *J* = 13.2 Hz, 2H), 1.34 - 0.81 (m, 15H), 0.75 - 0.63 (m, 2H), 0.58 - 0.44 (m, 2H). HPLC = 94.1% (214 nm), 96.7% (254 nm), t_R = 5.15 min. LC-MS: m/z = 475.0 $[M+H]^+$.

[00286] Example #12: was prepared following the procedure for **Example #11**, but using ethanamine in **step 4** and cyclopentanecarbonyl chloride in **step 6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.45 - 7.33 (m, 4H), 7.26 - 7.22 (m, 1H), 3.92 (dd, *J* = 14.1, 7.2 Hz, 2H), 3.35 (d, *J* = 13.5 Hz, 2H), 2.79 - 2.72 (m, 3H), 1.91 - 1.68 (m, 6H), 1.59 - 1.48 (m, 2H), 1.15 (t, *J* = 6.0 Hz, 3H), 0.78 - 0.38 (m, 4H). HPLC = 96.1% (214 nm), 99.0% (254 nm), t_R = 5.14 min. LC-MS: m/z = 473.1 $[M+H]^+$.

[00287] Example #14: was prepared following the procedure for **Example #11**, but using ethaneamine in **step 4** and cyclobutanecarbonyl chloride in **step 6**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.26 - 8.06 (m, 1H), 7.86 - 7.66 (m, 1H), 7.63 - 7.41 (m, 4H), 7.30 - 7.24 (m, 1H), 3.87 - 3.75 (m, 2H), 3.37 (d, *J* = 9.6 Hz, 1H), 3.23 - 3.00 (m, 1H), 2.82 (d, *J* = 13.8 Hz, 1H),

2.26 - 2.14 (m, 3H), 1.93 - 1.70 (m, 5H), 1.17 - 0.99 (m, 3H), 0.72 - 0.17 (m, 4H). HPLC = 95.7% (214 nm), 99.1% (254 nm), t_R = 4.88 min. LC-MS: m/z = 459.0 $[M+H]^+$.

[00288] Example #23: was prepared following the procedure for **Example #25**, but using sodium 3-trifluoromethylbenzenesulfinate in **step 1** and ethaneamine in **step 4**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (s, 1H), 8.06 - 8.03 (m, 1H), 7.76 - 7.36 (m, 5H), 3.99 - 3.96 (m, 2H), 3.78 - 3.76 (m, 2H), 3.31 - 3.30 (m, 2H), 2.58 - 2.56 (m, 4H), 1.18 - 1.03 (m, 12H). HPLC = 98.2% (214 nm), 95.9% (254 nm), t_R = 4.49 min. LC-MS: m/z = 499.0 $[M+H]^+$.

[00289] Example #22: was prepared following the procedure for **Example #23**, but using cyclobutanecarbonyl chloride in **step 6**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (s, 1H), 8.03 - 8.01 (m, 1H), 7.89 - 7.35 (m, 5H), 4.00 - 3.96 (m, 2H), 3.89 - 3.84 (m, 2H), 3.32 - 3.30 (m, 3H), 2.52 - 250 (m, 4H), 2.26 - 2.23 (m, 2H), 1.90 - 1.86 (m, 4H), 1.15 (t, J = 6.9 Hz, 3H). HPLC = 96.7% (214 nm), 97.6% (254 nm), t_R = 4.36 min. LC-MS: m/z = 497.0 $[M+H]^+$.

[00290] Example #13: was prepared following the procedure for **Example #25**, but replacing **step 4** with **steps 1** and **2** of **Scheme 21**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.64 - 7.52 (m, 4H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.59 (s, 2H), 3.76 - 3.62 (m, 4H), 3.31 - 3.13 (m, 2H), 1.15 - 1.05 (m, 12H). HPLC = 99.6% (214 nm), 99.7% (254 nm), t_R = 4.69 min. LC-MS: m/z = 447.1 $[M+H]^+$.

[00291] Example #5: was prepared following the procedure for **Example #25**, but using sodium 3-trifluoromethylbenzenesulfinate in **step 1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 - 7.55 (m, 6H), 7.20 (d, *J* = 8.4Hz, 6H), 4.05 - 3.95 (m, 2H), 3.34 - 3.26 (m, 2H), 3.12 - 2.95 (m, 1H), 2.75 - 2.654 (m, 2H), 2.42 - 2.35 (m, 2H), 1.09 (s, 9H), 0.98 - 0.78 (m, 2H), 0.61 - 0.57 (m, 2H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.49 min. LC-MS: m/z = 511.0 $[M+H]^+$.

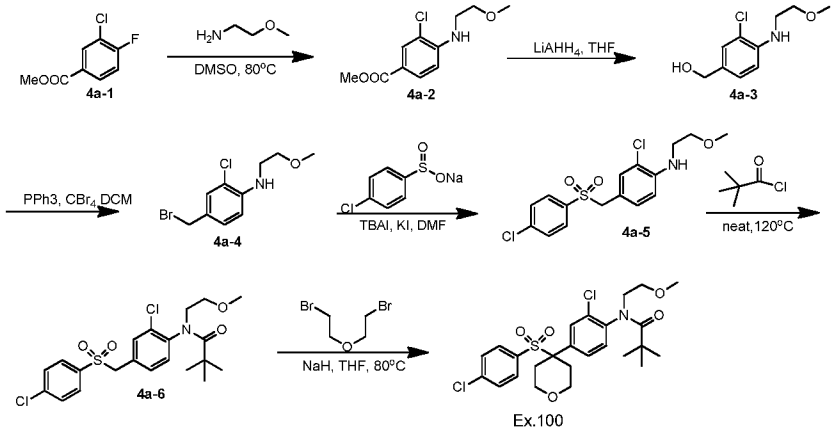
[00292] Example #102: was prepared following the procedure for **Example #25**, but using n-butyl lithium/ dihydro-2*H*-pyran-3(4H)-one in step 2 and ethaneamine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.5 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.39 - 7.36 (m, 2H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.23 - 7.20 (m, 2H), 4.51 - 4.47 (m, 1H), 4.16 - 4.12 (m, 1H), 3.89 - 3.84 (m, 1H), 3.65 (q, *J* = 7.0 Hz, 2H), 3.56 - 3.47 (m, 1H), 2.70 - 2.54 (m, 2H), 1.68 - 1.58 (m, 2H), 1.08 - 1.01 (m, 12H). HPLC = 96.2% (214 nm), 97.8% (254 nm), t_R = 4.53 min. LC-MS: m/z = 465.0 $[M+H]^+$.

[00293] Example #111: was prepared following the procedure for **Example #23**, but using propan-2-amine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.85 - 7.75 (m, 3H), 7.68 - 7.50 (m, 2H), 7.25 - 7.19 (m, 1H), 4.85 - 4.80 (m, 1H), 4.05 - 3.99 (m, 2H), 3.25 (t, *J* =

11.1 Hz, 2H), 2.70 - 2.57 (m, 2H), 2.44 - 2.38 (m, 2H), 1.15 - 1.01 (m, 15H). HPLC = 100% (214 nm), 99.3% (254 nm), t_R = 4.62 min. LC-MS: m/z = 513.0 $[M+H]^+$.

[00294] Example #17: was prepared following the procedure for **Example #11**, cyclopropylmethylamine in **step 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.7 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.41 - 7.32 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 1H), 3.60 (d, *J* = 3.9 Hz, 2H), 3.38 (d, *J* = 10.5 Hz, 2H), 2.70 (d, *J* = 13.8 Hz, 2H), 1.09 - 0.98 (m, 10H), 0.66 - 0.65 (m, 2H), 0.42 - 0.38 (m, 4H), 0.03 - 0.01 (m, 2H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.32 min. LC-MS: m/z = 487.0 $[M+H]^+$.

[00295] Scheme 4a: synthesis of Example #100



[00296] Step 1: To a solution of compound **4a-1** (5 g, 26 mmol) in DMSO (20 mL) was 2-methoxyethylamine (7ml, 80mmol). The mixture was stirred overnight at 80^{0}C, Subsequently the reaction solution was concentrated to the residue. The residue was purified by silica-gel column chromatography, eluting with PE/EA=10/1, to give the desired product **2**. LC-MS: m/z = 244 $[M+H]^+$.

[00297] Step 2: Compound **4a-2** (5 g, 20 mmol) was dissolved in THF (20 ml) and cooled to 0^{0}C. 1.0M lithium tetrahydroaluminate in THF was added and the reaction stirred for 2 hrs. The reaction was quenched at 0^{0}C by adding 0.5 ml water, followed by addition of 1.0 ml of 10% NaOH and 1.5 ml water. The solution was filtered and solvent removed in vacuo. LC-MS: m/z = 216 $[M+H]^+$.

[00298] Step 3: PPh_3 (1.8 g, 7.0 mmol) and CBr_4 (2.3 g, 7.0 mmol) was added to a solution of compound **4a-3** (1.0 g, 6.4 mmol) in DCM (50 mL). The mixture was stirred for 0.5h at room temperature. Water (50 mL) was added. The mixture was extracted with DCM (50 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4,

concentrated, and purified by flash column chromatography (PE/EA=101) to give the product **4a-4**. LC-MS: m/z = 279 $[M+H]^+$.

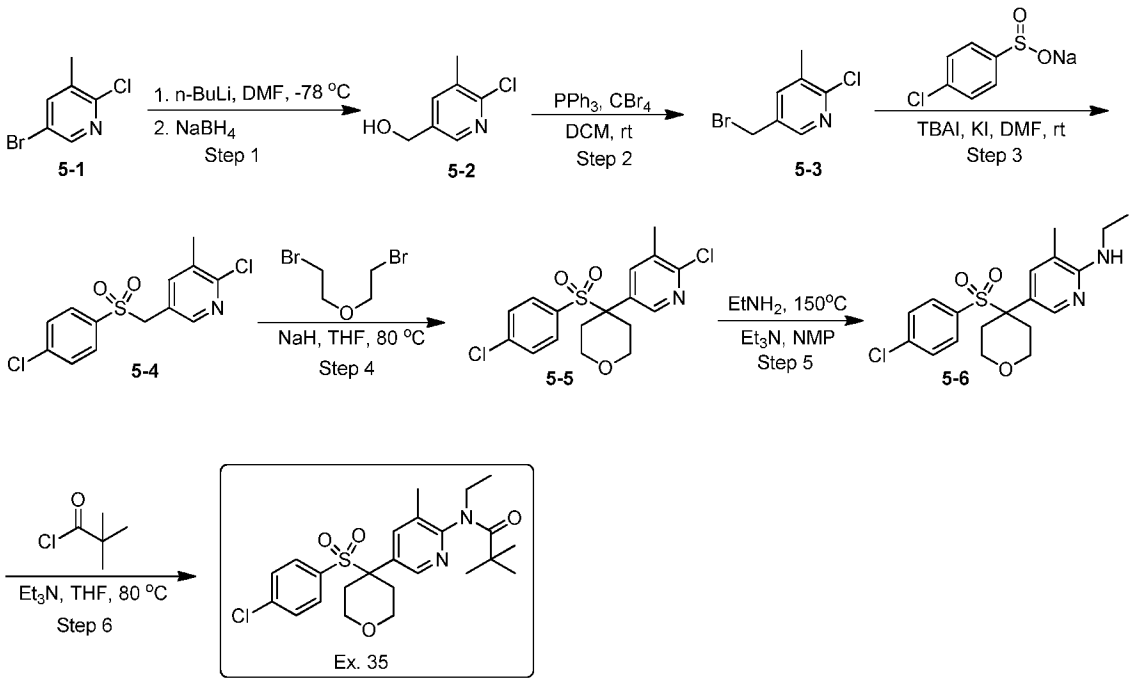
[00299] Step 4: The same procedure with the **step 4** of **Scheme 1** was applied to the preparation of compound **4a-5**. LC-MS: m/z = 375 $[M+H]^+$.

[00300] Step 5: The same procedure with the **step 4** of **Scheme 3** was applied to the preparation of compound **4a-6**. LC-MS: m/z = 459 $[M+H]^+$.

[00301] Example #100: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of compound **Example #100**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.27 (m, 6H), 7.25 - 7.11 (m, 1H), 4.38 - 4.35 (m, 1H), 4.05 - 3.98 (m, 2H), 3.52 - 3.48 (m, 2H), 3.42 - 3.38 (m, 5H), 3.07 - 3.05 (m, 1H), 2.66 - 2.63 (m, 2H), 2.38 - 2.32 (m, 2H), 1.08 (s, 9H). HPLC = 99.5% (214 nm), 100% (254 nm), t_R = 4.77 min. LC-MS: m/z = 527.8 $[M+H]^+$.

[00302] Example #105: was prepared following the procedure for **Example #100**, except cyclopropylmethanamine was used in **step 1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.28 (m, 6H), 7.14 - 7.10 (m, 1H), 4.22 - 4.15 (m, 1H), 4.02 - 3.98 (m, 2H), 3.27 (t, *J* = 11.8 Hz, 2H), 2.84 - 2.60 (m, 3H), 2.38 - 2.33 (m, 2H), 1.33 - 1.04 (m, 9H), 0.98 - 0.88 (m, 1H), 0.47 - 0.36 (m, 2H), 0.16 - 0.09 (m, 1H), -0.06 - -0.14 (m, 1H). HPLC = 99.4% (214 nm), 99.0% (254 nm), t_R = 5.24 min. LC-MS: m/z = 523.9 $[M+H]^+$.

[00303] Scheme 5. Synthesis of Example #35



[00304] **Step 1**: n-BuLi (4.8 mL, 12 mmol) was added dropwise to a solution of 5-bromo-2-chloro-3-methylpyridine (2.1 g, 10.0 mmol) in THF (40 mL) at -78 °C. Then DMF (1.5 g, 20 mmol) was added, and stirred for another 2 hours at -78 °C. Methanol (12 mL) was added to quench the reaction. $NaBH_4$ (1.1 g, 30 mmol) was added, and stirred for 0.5h. Ice water (40 mL) was added. The mixture was extracted with DCM (30 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (PE/EA=2/1) to give the product **5-2** as yellow oil. LC-MS: m/z = 158.1 $[M+H]^+$.

[00305] **Step 2**: PPh_3 (0.18 g, 0.70 mmol) and CBr_4 (0.23 g, 0.70 mmol) was added to a solution of compound **5-2** (0.1 g, 0.64 mmol) in DCM (10 mL). The mixture was stirred for 0.5h at room temperature. Water (15 mL) was added. The mixture was extracted with DCM (15 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=101) to give the product **5-3** as white solid. LC-MS: m/z = 220.0 $[M+H]^+$.

[00306] **Step 3**: The same procedure with the **step 4** of **Scheme 1** was applied to the preparation of compound **5-4**. LC-MS: m/z = 316.0 $[M+H]^+$.

[00307] **Step 4**: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of compound **5-5**. LC-MS: m/z = 385.9 $[M+H]^+$

[00308] **Step 5**: Compound **5-5** (0.37 g, 0.96 mmol), Et_3N (0.48 g, 4.8 mmol) and $EtNH_2$ (70% in water, 0.22 g, 4.8 mmol) in NMP (10 mL) was sealed in tube, and stirred for 6 hours at 150 °C. The solvent was removed by reduced pressure. Water (20 mL) was added. The mixture was extracted with EA (10 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=2/1) to give the product **5-6** as yellow oil. LC-MS: m/z = 395.1 $[M+H]^+$.

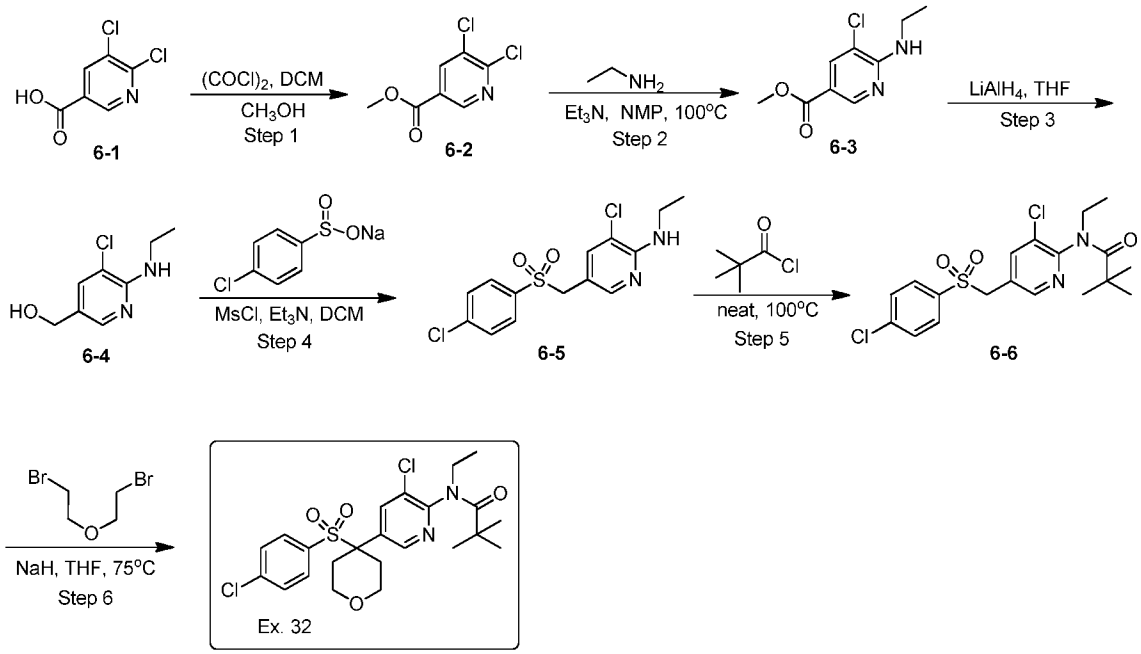
[00309] **Example #35:** Pivaloyl chloride (0.38 g, 3.15 mmol) was added to a solution of compound **5-6** (0.25 g, 0.63 mmol) and Et_3N (0.32 mmol, 3.15 mmol) in THF (20 mL). The mixture was stirred at 80 °C overnight. The mixture was cooled to room temperature. Water (20 mL) was added. The mixture was extracted with DCM (15 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by pre-TLC and pre-HPLC to give the product as white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.58 (s, 1H), 7.41 - 7.39 (m, 2H), 7.25 - 7.22 (m, 4H), 4.02 - 3.98 (m, 2H), 3.67 - 3.65 (m, 2H), 3.32 - 3.24 (m, 2H), 2.51 - 2.37 (m, 7H), 1.09 - 0.96 (m, 12H). HPLC =

98.5% (214 nm), 98.7% (254 nm), t_R = 4.31 min. LC-MS: m/z = 479.2 $[M+H]^+$.

[00310] Example #113: was prepared as described in **Scheme 5**, except using cyclobutylamine in step 1. 1H NMR (300 MHz, CDCl3) δ 7.97 (d, J = 2.1 Hz, 1H), 7.65 (s, 1H), 7.34 (q, J = 8.4 Hz, 4H), 4.76 (s, 1H), 4.03 (d, J = 10.8 Hz, 2H), 3.234 – 3.26 (m, 2H), 2.75 – 2.60 (m, 2H), 2.44 – 2.39 (m, 2H), 2.22 (s, 3H), 2.01 (bs, 2H), 1.71 – 1.56 (m, 4H), 1.06 (s, 9H). LC-MS: m/z = 505.0 [M+H]+.

[00311] Example #114: was prepared as described in **Scheme 5**, except using propane-2-amine in step 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 2.4 Hz, 1H), 7.61 (s, 1H), 7.33 (q, J = 8.7 Hz, 4H), 4.37 (bs, 1H), 4.00 (d, J = 11.7 Hz, 2H), 3.27 (t, J = 11.7 Hz, 2H), 2.71 – 2.56 (m, 2H), 2.46 – 2.23 (m, 5H), 1.37 – 0.88 (m, 15H). LC-MS: m/z = 493.1 $[M+H]^+$.

[00312] Scheme 6. Synthesis of Example #32



[00313] Step 1: A mixture of compound **6-1** (4 g, 20.8 mmol) in DCM (100 mL) was added oxalyl chloride (10.5 g, 83.2 mmol) dropwise. The resulting mixture was stirred at room temperature for 12 hours. Then methanol (6.7 g, 208 mmol) was added into the above solution at 0 °C. After being stirred at room temperature for another 0.5 hours, the mixture was washed with H_2O (100 mL), extracted with DCM (100 mL x 2), the organic phase was dried over anhydrous Na_2SO_4 and concentrated, purified by flash column chromatography to give product **6-2** as white solid.

[00314] Step 2: Compound **6-2** (3.2 g, 15.5 mmol), Et_3N (7.8 g, 77.5 mmol) and $EtNH_2$ (70% in water, 3.5 g, 77.5 mmol) was added into NMP (50 mL). The mixture was stirred for

6 hours at 100 °C. The solvent was removed by reduced pressure. Water (80 mL) was added. The mixture was extracted with EtOAc (80 mL x 3). Combined organic layers was dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography to give the product **6-3** as white solid. LC-MS: m/z = 215.0 $[M+H]^+$.

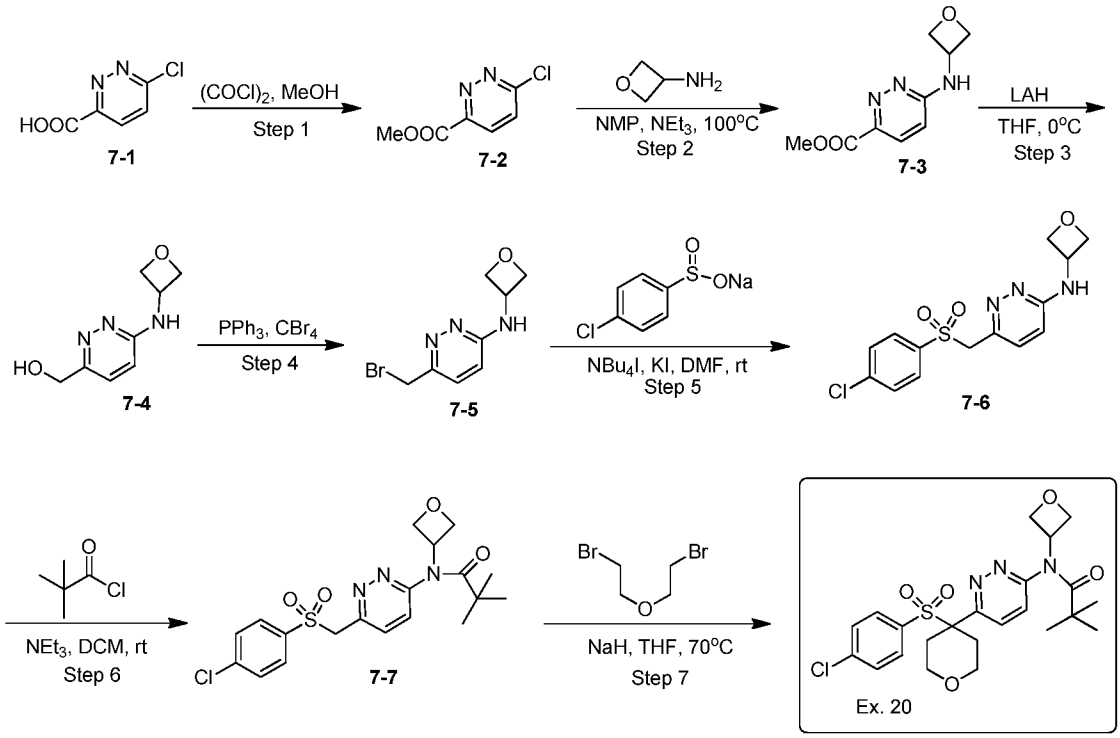
[00315] Step 3: To a mixture of compound **6-3** (1.7 g, 8 mmol) in THF (80 mL) was added LAH (0.6 g, 16 mmol) in portions at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. Then the reaction was quenched with H_2O (2 mL) and filtered. The filtrate was concentrated to give crude product **6-4** as yellow oil. LC-MS: m/z = 187.1 $[M+H]^+$.

[00316] Step 4: To a mixture of compound of **6-4** (0.6 g, 3.2 mmol), sodium 4-chlorobenzenesulfinate (0.76 g, 3.8 mmol) and TEA (0.65 g, 6.4 mmol) in DCM (40 mL) was added methanesulfonyl chloride (0.43 g, 3.8 mmol). Then the mixture was stirred for 2 hours at room temperature. Water (40 mL) was added. The mixture was extracted with EtOAc (40 mL x 2). Combined organic layers was dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography to give the product **6-5** as white solid. LC-MS: m/z = 345.0 $[M+H]^+$.

[00317] Step 5: To compound of **6-5** (0.2 g, 0.58 mmol) was added pivaloyl chloride (5 mL), the mixture was stirred for 12 hours at 100 °C. After removed of most of pivaloyl chloride, water (10 mL) was added. The mixture was extracted with EtOAc (10 mL x 3). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the product **6-6** as yellow solid. LC-MS: m/z = 429.0 $[M+H]^+$.

[00318] Example #32: To a mixture of compound **6-6** (0.22 g, 0.51 mmol) and NaH (40 mg, 1.02 mmol) in THF (20 mL) was added 1-(2-bromoethoxy)-2-bromoethane (176 mg, 0.76 mmol) at rt. The resulting mixture was stirred for 6 hours at 75°C, then quenched with H_2O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by preparative TLC to give the as white solid. ^1H NMR (300 MHz, CDCl3) δ 8.04 - 7.37 (m, 6H), 4.04 - 3.25 (m, 6H), 2.62 - 2.35 (m, 4H), 1.13 - 1.10 (m, 12H); HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.77 min. LC-MS: m/z = 498.9 $[M+H]^+$.

[00319] Scheme 7. Synthesis of Example #20



[00320] Step 1: To a mixture of compound **7-1** (4.14 g, 26.1 mmol) in DCM (100 mL) was added oxalyl chloride (3.98 g, 31.3 mmol) dropwise. DMF (0.05 mL) was added and the resulting mixture was stirred at room temperature until the compound **7-1** was dissolved. Then MeOH (2 mL) was added dropwise and stirred for another 0.5 hr. After being washed with brine (100 mL), the mixture was dried over anhydrous Na_2SO_4 and concentrated to give crude product. The crude product was purified by silica-gel column chromatography (eluting with PE/EA = 4/1) to yield the desired product **7-2** as white solid. LC-MS: m/z = 173.1 $[M+H]^+$.

[00321] Step 2: A mixture of compound **7-2** (1.73 g, 10 mmol), oxetan-3-amine (0.88 g, 12 mmol) and TEA (4.04 g, 40 mmol) in NMP (20 mL) was stirred overnight at 100°C. The mixture was concentrated to give the residue. The residue was purified by silica-gel column chromatography (eluting with PE/EA = 10/1) to yield the desired product **7-3** as yellow solid. LC-MS: m/z = 210.1 $[M+H]^+$.

[00322] Step 3: To a mixture of compound **7-3** (3.3 g, 15.7 mmol) in THF (50 mL) was added LAH (1.194 g, 31.4 mmol) in portions at 0 °C. The resulting mixture was stirred at 0 °C for 2 hrs. Then the reaction was quenched with H_2O (2 mL) and filtered. The filtrate was concentrated to give crude product. The crude product was purified by silica-gel column chromatography (eluting with MeOH/EA = 1/10) to yield the desired product **7-4** as white

solid. LC-MS: m/z = 182.0 $[M+H]^+$.

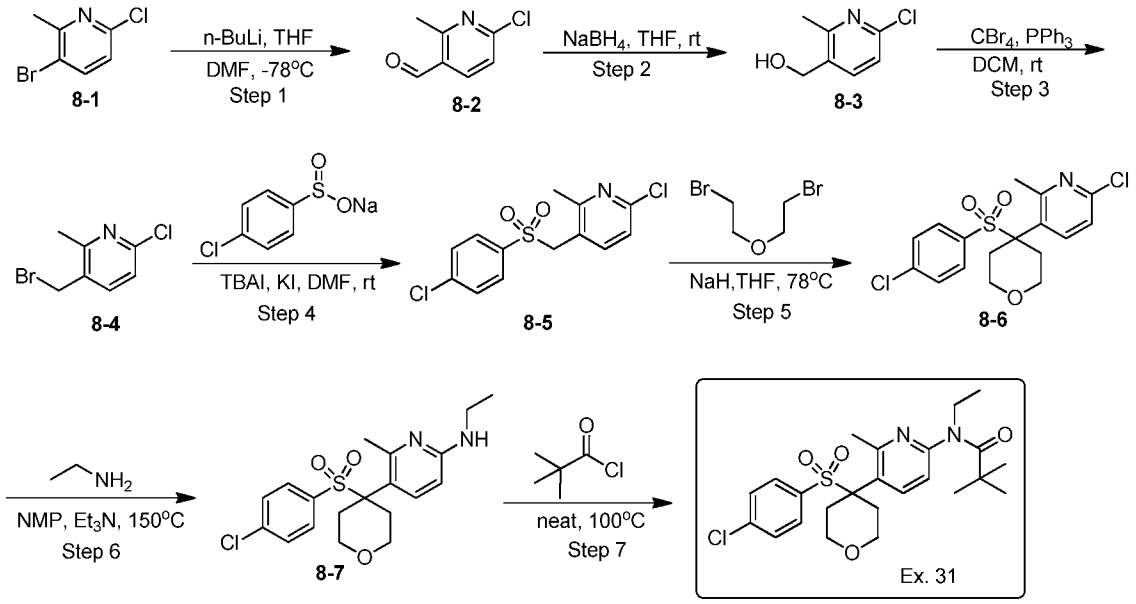
[00323] **Step 4**: To a solution of compound **7-4** (0.415 g, 2.29 mmol), CBr_4 (0.913 g, 2.75 mmol) in DCM (50 mL) was added PPh_3 (0.78 g, 2.977 mmol) in portions at r.t. The resulting mixture was stirred at r.t. for 0.5 hrs. Then the reaction solution was used directly in step 5 of **Scheme 7**. LC-MS: m/z =244.0 $[M+H]^+$.

[00324] **Step 5**: The solution of compound **7-5** prepared from last step was added to a mixture of sodium 4-chlorobenzenesulfinate (0.578 g, 2.75 mmol), Bu_4NI (0.339 g, 0.92 mmol), KI (0.42 g, 3.53 mmol) in DMF (50 mL). The resulting mixture was stirred at r.t. for 1 hr. Then it was washed with brine (100 mL x 2), the mixture was dried over anhydrous Na_2SO_4 and concentrated to give crude product. The crude product was purified by flash column chromatography (eluting with DCM/MeOH = 20/1) to yield the desired product **7-6** as white solid. LC-MS: m/z = 339.9 $[M+H]^+$.

[00325] **Step 6**: To a solution of compound **7-6** (355 mg, 1.04 mmol), TEA (315 mg, 3.12 mmol) in DCM (20 mL) was added pivaloyl chloride (151 mg, 1.25 mmol) dropwise at r.t. After being stirred at r.t. for 1 hr, the solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product. The crude product was purified by flash column chromatography (eluting with DCM/MeOH = 20/1) to yield the desired product **7-7** as white solid. LC-MS: m/z = 424.0 $[M+H]^+$.

[00326] **Example #20:** A mixture of compound **7-7** (100 mg, 0.24 mmol), NaH (30 mg, 70%w/w, 0.88 mmol), 1-bromo-2-(2-bromoethoxy)ethane (170 mg, 0.72 mmol) in THF (50 mL) was stirred at 72 °C for 4 hr. Then it was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give crude product. The crude product was purified by prep TLC and flash column chromatography (eluting with DCM/MeOH = 20/1) to yield the desired product as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.27 - 7.24 (m, 2H), 5.38 - 5.29 (m, 1H), 4.79 (t, *J* = 7.2 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 2H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.29 - 3.12 (m, 2H), 2.69 (d, *J* = 3.6 Hz, 4H), 1.04 (s, 9H). HPLC = 92.9% (214 nm), 87% (254 nm), t_R = 3.99 min. LC-MS: m/z = 494.0 $[M+H]^+$.

[00327] Scheme 8. Synthesis of Example #31



[00328] Step 1: Under nitrogen atmosphere, to a solution of compound **8-1** (1.0 g, 5 mmol) in dry THF (30 mL) was added n-Butyllithium, 2.5 M solution in THF (3 mL, 7.5 mmol) dropwise under minus 78 degree. The solution was stirred at -78 degree for 10 min, followed by addition of dry DMF (0.73 g, 10 mmol). The mixture was stirred for 30 min at this temperature and then quenched with H_2O (30 mL), extracted with EA (30 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give product **8-2** as yellow oil. LC-MS: m/z = 156.1 $[M+H]^+$.

[00329] Step 2: A mixture of compound **8-2** (0.55 g, 3.5 mmol), $NaBH_4$ (0.4 g, 10.5 mmol) in dry THF (40 mL) was stirred at rt for 6 hours. After quenched with H_2O (30 mL), the mixture was extracted with EtOAc (30 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography to give product **8-3** as yellow oil. LC-MS: m/z = 158.0 $[M+H]^+$.

[00330] Step 3: PPh_3 (0.333 g, 1.27 mmol) and CBr_4 (0.423 g, 1.27 mmol) was added to the solution of **8-3** (0.2 g, 1.27 mmol) in DCM (20 mL). The mixture was stirred for 0.5h at room temperature. Concentrated and purified by flash column chromatography to give the product **8-4** as yellow solid. LC-MS: m/z = 219.9 $[M+H]^+$.

[00331] Step 4: Compound **8-4** (0.18 g, 0.83 mmol), sodium 4-chlorobenzenesulfinate (0.486 g, 2.45 mmol), TBAI (0.136 g, 0.37 mmol) and KI (0.06 g, 0.37 mmol) in DMF (20 mL) was stirred for 1 hour at rt. After removed of most of DMF, water (20 mL) was added. The mixture was extracted with EtOAc (20 mL x 2). Combined organic layers was dried over

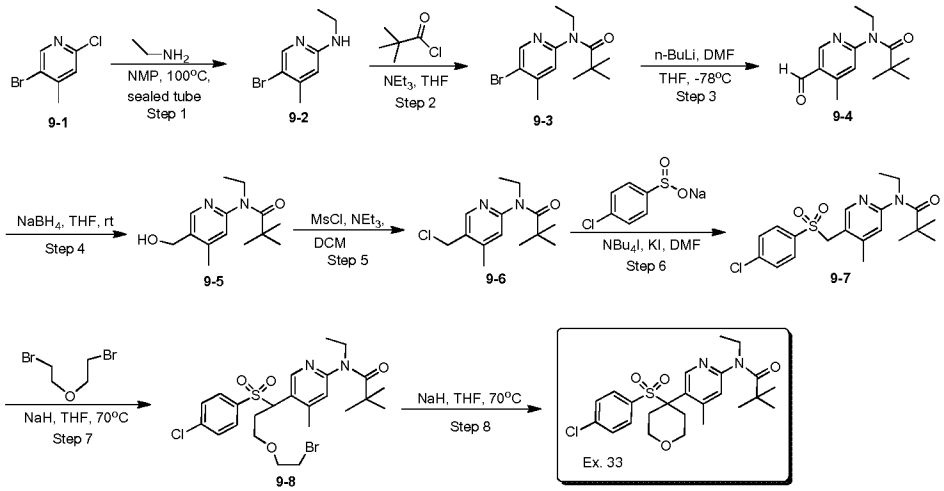
anhydrous Na_2SO_4, concentrated and purified by flash column chromatography to give product **8-5** as white solid. LC-MS: m/z = 315.9 $[M+H]^+$.

[00332] **Step 5**: To a mixture of compound **8-5** (200 mg, 0.63 mmol) and NaH (55 mg, 1.26 mmol) in THF (12 mL) was added 1-(2-bromoethoxy)-2-bromoethane (220 mg, 0.95 mmol) at rt. The resulting mixture was stirred for 12 hours at 75°C, then quenched with H_2O (15 mL), extracted with EtOAc (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by preparative TLC to give product **8-6** as yellow solid. LC-MS: m/z = 386.1 $[M+H]^+$.

[00333] **Step 6**: Compound **8-6** (60 mg, 0.155 mmol), Et_3N (80 mg, 0.78 mmol) and $EtNH_2$ (70% in water, 35 mg, 0.78 mmol) was added into NMP (5 mL). The mixture was stirred for 12 hours at 150 °C. The solvent was removed by reduced pressure. Water (10 mL) was added. The mixture was extracted with EtOAc (10 mL x 2). Combined organic layers was dried over Na_2SO_4, concentrated and purified by pre-TLC to give the product **8-7** as white solid. LC-MS: m/z = 395.1 $[M+H]^+$.

[00334] **Example #31:** To compound **8-7** (15 mg, 0.038 mmol) was added pivaloyl chloride (5 mL), the mixture was stirred for 12 hours at 100 °C. After removed of most of pivaloyl chloride, water (10 mL) was added. The mixture was extracted with EtOAc (10 mL x 2). Combined organic layers was dried over anhydrous Na_2SO_4, concentrated and purified by pre-TLC to give the product as white solid. ^1H NMR (300 MHz, CDCl3) δ 7.52 - 7.07 (m, 6H), 4.04 - 3.24 (m, 6H), 2.60 - 2.49 (m, 7H), 1.10 - 1.04 (m, 12H). HPLC = 94.2% (214 nm), 96.7% (254 nm), t_R = 4.35 min. LC-MS: m/z = 479.0 $[M+H]^+$.

[00335] **Scheme 9. Synthesis of Example #33**



[00336] **Step 1**: A mixture of compound **9-1** and aqueous $EtNH_2$ (10 mL) in NMP (5 mL) was stirred for 3 days at 80°C in a sealed tube, then concentrated. The residue was diluted with EtOAc (50 mL), washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography, eluting with PE/EA = 4/1 to give target compound **9-2** as yellow oil. LC-MS: m/z = 215.0 $[M+H]^+$.

[00337] **Step 2**: To a mixture of compound **9-2** (1.89 g, 8.22 mmol) and NEt_3 (2.49 g, 24.7 mmol) in THF (20 mL) was added pivaloyl chloride (1.98 g, 16.4 mmol) at rt. The resulting mixture was stirred for 1h at rt, then diluted with EtOAc (50 mL), washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1 to give target compound **9-3** as yellow oil. LC-MS: m/z = 299.0 $[M+H]^+$.

[00338] **Step 3**: Under nitrogen atmosphere, to a solution of Compound **9-3** (0.5 g, 1.68 mmol) in dry THF (20 mL) was added n-Butyllithium, 2.5 M solution in THF (1.0 mL, 2.52 mmol) dropwise under minus 80 degree. The solution was stirred at -80 degree for 5 min, followed by addition of dry DMF (0.24 g, 3.36 mmol). The mixture was stirred for another 10 min at this temperature and then quenched with H_2O (20 mL), extracted with EtOAc (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product **9-4** as yellow oil. LC-MS: m/z = 249.2 $[M+H]^+$.

[00339] **Step 4**: A mixture of Compound **9-4** (0.47 g, 1.91 mmol), $NaBH_4$ (0.22 g, 5.72 mmol) in dry THF (20 mL) was stirred at r.t for 2h. After quenched with H_2O (20 mL), the mixture was extracted with EtOAc (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography, eluting with PE/EA = 2/1 to give target compound **9-5** as yellow oil, LC-MS: m/z = 251.1 $[M+H]^+$.

[00340] **Step 5**: To a mixture of compound **9-5** (160 mg, 0.64 mmol) and NEt_3 (0.19 g, 1.92 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (147 mg, 1.28 mmol) at rt. The resulting mixture was stirred for 1h at rt, then concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1 to give target compound **9-6** as colorless oil. LC-MS: m/z = 269.1 $[M+H]^+$.

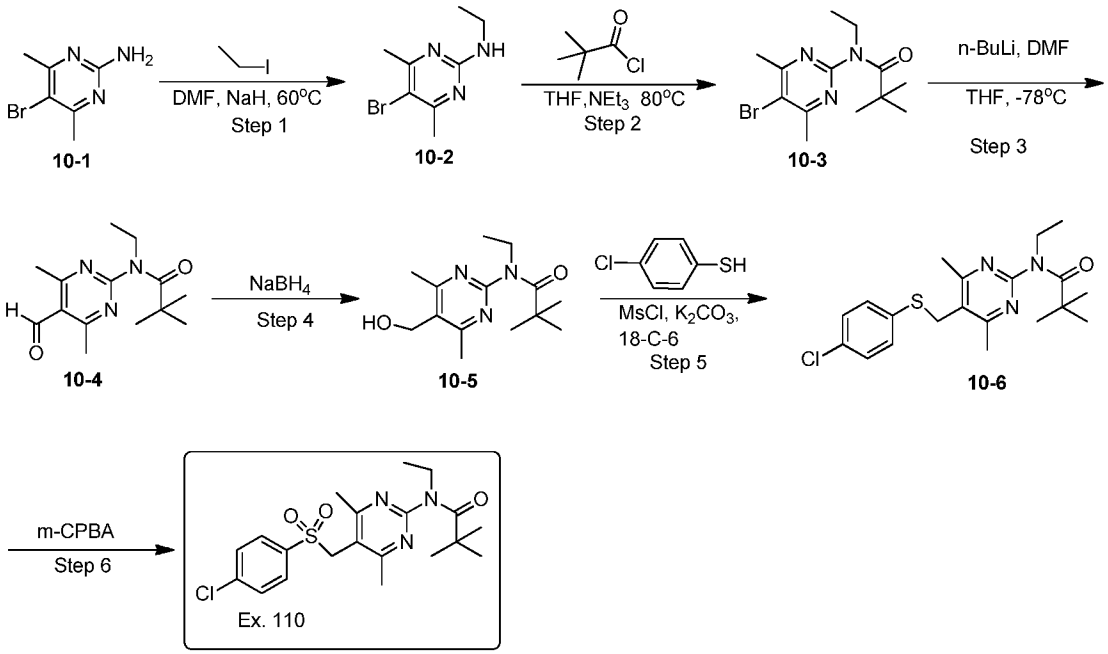
[00341] **Step 6**: A mixture of compound **9-6** (170 mg, 0.63 mmol), sodium 4-chlorobenzenesulfinate (189 mg, 0.96 mmol), KI (53 mg, 0.32 mmol) and tetrabutyl ammonium iodide (117 mg, 0.32 mmol) in DMF (10 mL) was stirred for 2h at rt. After being diluted with EtOAc (50 mL), the reaction mixture was washed with H_2O (10 mL X 3), brine

(10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative column chromatography eluting with PE/EA = 4/1 to give target compound **9-7** as yellow oil. LC-MS: m/z = 409.0 $[M+H]^+$.

[00342] Step 7: To a mixture of compound **9-7** (200 mg, 0.49 mmol) and NaH (59 mg, 2.45 mmol) in THF (10 mL) was added 1-(2-bromoethoxy)-2-bromoethane (340 mg, 1.47 mmol) at rt. The resulting mixture was stirred for 5h at 70°C, then quenched with H_2O (10 mL), extracted with EtOAc (20 mL X 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC to give target compound **9-8** as yellow oil. LC-MS: m/z = 559.0 $[M+H]^+$.

[00343] Example #33: A mixture of compound **9-8** (180 mg, 0.32 mmol) and NaH (15 mg, 0.64 mmol) in THF (10 mL) was added 1-(2-bromoethoxy)-2-bromoethane (340 mg, 1.47 mmol) at rt. The resulting mixture was stirred for 3h at 70°C, then quenched with H_2O (10 mL), extracted three times with EtOAc (20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC to give target compound **Example 33** as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.48 - 7.35 (m, 4H), 7.05 (s, 1H), 4.05 - 4.00 (m, 2H), 3.79 (q, J = 6.9 Hz, 2H), 3.38 - 3.26 (m, 2H), 3.00 - 2.52 (m, 7H), 1.23 - 1.00 (m, 12H). HPLC = 96.5% (214 nm), 96.7% (254 nm), t_R = 4.39 min. LC-MS: m/z = 479.0 $[M+H]^+$.

[00344] Scheme 10. Synthesis of Example #110



[00345] **Step 1**: A mixture of compound **10-1** (2 g, 9.9 mmol), iodoethane (2 g, 12.9 mmol) and NaH (0.48 g, 19.8 mmol) in DMF (20 mL) was stirred for 2h at 60°C. After being diluted with EtOAc (100 mL), the reaction mixture was washed with H_2O (20 mL X 3), brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 10/1 to give target compound **10-2** as yellow oil. LC-MS: m/z = 230.0 $[M+H]^+$.

[00346] **Step 2**: A mixture of compound **10-2** (1.41 g, 8.22 mmol), NEt_3 (1.86 g, 18.4 mmol) and pivaloyl chloride (1.98 g, 16.4 mmol) in THF (20 mL) was added pivaloyl chloride (1.48 g, 12.3 mmol) was stirred for 3 days at 60°C, then diluted with EtOAc (50 mL), washed with H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1 to give target compound **10-3** as yellow oil. LC-MS: m/z = 314.0 $[M+H]^+$.

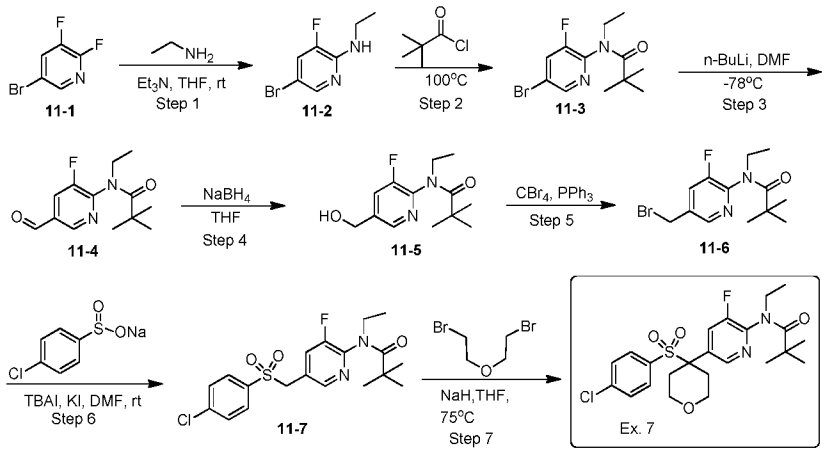
[00347] **Step 3**: Under nitrogen atmosphere, to a solution of Compound **10-3** (1.48 g, 4.73 mmol) in dry THF (20 mL) was added n-Butyllithium, 2.5 M solution in THF (2.8 mL, 7.09 mmol) dropwise under minus 80 degree. The solution was stirred at -80 degree for 5 min, followed by addition of dry DMF (0.69 g, 9.46 mmol). The mixture was stirred for another 10 min at this temperature and then quenched with H_2O (20 mL), extracted with EtOAc (20 mL X 3).The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to give crude product **10-4** as a yellow oil. LC-MS: m/z = 264.2 $[M+H]^+$

[00348] **Step 4**: A mixture of compound **10-4** (1.1 g, 4.18 mmol), $NaBH_4$ (0.48 g, 12.5 mmol) in dry THF (10 mL) was stirred at r.t for 2h. After quenched with H_2O (20 mL), the mixture was extracted with EtOAc (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography, eluting with PE/EA = 2/1 to give target compound **10-5** as yellow oil. LC-MS: m/z = 266.1 $[M+H]^+$.

[00349] **Step 5**: A mixture of compound **10-5** (0.45 g, 1.70 mmol), 4-chlorobenzenethiol (0.29 g, 2.04 mmol), K_2CO_3 (0.70 g, 5.09 mmol), methanesulfonyl chloride (0.23 g, 2.04 mmol), KI (0.42 g, 2.55 mmol) and 18-C-6 (45 mg, 0.17 mmol) in THF (20 mL) was stirred for 3 days at rt, then diluted with EtOAc (50 mL), washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1 to give target compound **10-6** as colorless oil. LC-MS: m/z = 392.0 $[M+H]^+$.

[00350] Example #110: To a solution of compound **10-6** (35 mg, 0.09 mmol) in DCM (5 mL) was added m-CPBA (46 mg, 0.27 mmol) at rt. The reaction mixture was stirred at rt for 2 hr, then diluted with EtOAc (10 mL), washed with 4N NaOH (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative column chromatography eluting with PE/EA = 2/1 to give target compound **Example #110** as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 - 7.51 (m, 4H), 4.44 (s, 2H), 3.91 (q, J = 7.1 Hz, 2H), 2.34 (s, 6H), 1.32 - 1.01 (m, 12H). HPLC = 99.2% (214 nm), 99.4% (254 nm), t_R = 4.78 min. LC-MS: m/z = 423.9 $[M+H]^+$.

[00351] Scheme 11. Synthesis of Example #7



[00352] Step 1: Compound **11-1** (2 g, 10 mmol), Et_3N (2 g, 20 mmol) and $EtNH_2$ (70% in water, 0.68 g, 15 mmol) was added into THF (30 mL), the mixture was stirred for 6 hours at rt. The solvent was removed by reduced pressure. Water (30 mL) was added. The mixture was extracted with EtOAc (30 mL x 3). Combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography to give the product **11-2** as a yellow oil. LC-MS: m/z = 218.9 $[M+H]^+$.

[00353] Step 2: To a compound of **11-2** (1.35 g, 6.2 mmol) was added pivaloyl chloride (5 mL), the mixture was stirred for 12 hours at 100 °C. After cooling to room temperature, water (10 mL) was added. The mixture was extracted with EA (10 mL x 2). Combined organic layers was dried over Na_2SO_4, concentrated and purified by flash column chromatography to give product **11-3** as a white solid. LC-MS: m/z = 302.9 $[M+H]^+$.

[00354] Step 3: Under nitrogen atmosphere, to a solution of compound **11-3** (0.8 g, 2.64 mmol) in dry THF (30 mL) was added n-Butyllithium, 2.5 M solution in THF (2.1 mL, 5.28

mmol) dropwise under minus 78 degree. The solution was stirred at -78 degree for 10 min, followed by addition of dry DMF (0.73 g, 10 mmol). The mixture was stirred for 30 min at this temperature and then quenched with H_2O (30 mL), extracted with EA (30 mL x 2).The combined organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography to give product **11-4** as a yellow oil. LC-MS: m/z = 253.1 $[M+H]^+$.

[00355] Step 4: A mixture of compound **11-4** (0.44 g, 1.74 mmol), $NaBH_4$ (0.132 g, 3.48 mmol) in dry THF (20 mL) was stirred at rt for 6 hours. After quenched with H_2O (30 mL), the mixture was extracted with EA (30 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography to give product **11-5** as a yellow oil. LC-MS: m/z = 255.1 $[M+H]^+$.

[00356] Step 5: PPh_3 (0.215 g, 0.82 mmol) and CBr_4 (0.27 g, 0.82 mmol) was added to a solution of compound **11-5** (0.2 g, 0.82 mmol) in DCM (20 mL). The mixture was stirred for 0.5h at room temperature. Concentrated and purified by flash column chromatography to give the product **11-6** as a yellow solid. LC-MS: m/z = 317.0 $[M+H]^+$.

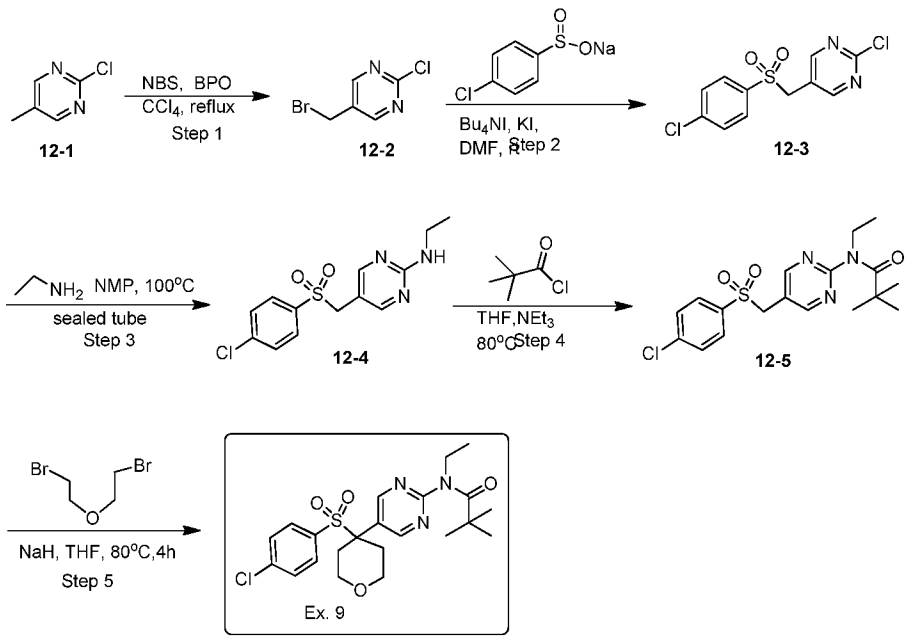
[00357] Step 6: Compound **11-6** (0.12 g, 0.31 mmol), sodium 4-chlorobenzenesulfinate (67 mg, 0.34 mmol), TBAI (37 mg, 0.1 mmol) and KI (17 mg, 0.1 mmol) in DMF (10 mL) was stirred for 1 hour at rt. After removed of most of DMF, water (20 mL) was added. The mixture was extracted with EA (20 mL x 2). Combined organic layers was dried over Na_2SO_4, concentrated and purified by flash column chromatography to give product **11-7** as a white solid. LC-MS: m/z = 412.9 $[M+H]^+$.

[00358] Example #7: To a mixture of compound **11-7** (75 mg, 0.18 mmol) and NaH (15 mg, 0.36 mmol) in THF (10 mL) was added 1-(2-bromoethoxy)-2-bromoethane (63 mg, 0.27 mmol) at rt. The resulting mixture was stirred for 12 hours at 75°C, then quenched with H_2O (15 mL), extracted with EA (15 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated and purified by preparative TLC to give product as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 - 7.37 (m, 6H), 4.04 - 4.01 (m, 2H), 3.80 - 3.78 (m, 2H), 3.33 - 3.29 (m, 2H), 2.63 - 2.59 (m, 2H), 2.38 - 2.34 (m, 2H) 1.18 - 1.10 (s, 12H). HPLC = 97.3% (214 nm), 98.4% (254 nm), t_R = 4.61 min. LC-MS: m/z = 483.1 $[M+H]^+$.

[00359] Example #230: was prepared as described in **Scheme 11**, using (*R*)-1-cyclohexylethanamine in **step 1**. ^{1}HNMR: (400 MHz, MeOD) δ: 8.13 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 11.2, 2.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 4.29-4.27 (m, 1H), 3.99-3.95 (m, 2H), 3.26-3.19 (m, 2H), 2.56-2.52 (m, 4H), 2.15-2.12 (m, 1H), 1.76-1.66 (m, 5H), 1.22-0.91 (m, 17H). LCMS (ESI): (M+H: 565).

[00360] Example #231: was prepared as described in **Scheme 11**, using phenylethylamine in **step 1**. ^{1}HNMR: (400 MHz, MeOD) δ: 8.11 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.24-7.13 (m, 6H), 5.78-5.73 (m, 1H), 3.96-3.88 (m, 2H), 3.16-3.13 (m, 1H), 3.04-3.01 (m, 1H), 2.50-2.44 (m, 4H), 1.53 (d, J = 4.2 Hz, 3H), 1.02 (s, 9H). LCMS (ESI): (M+H: 581).

[00361] Scheme 12. Synthesis of Examples #2 and #9



[00362] Step 1: A mixture of compound **12-1** (1.18 g, 9.18 mmol), NBS (1.96 g, 11.0 mmol) and benzoyl peroxide (0.11 g, 0.46 mmol) in CCl_4 (30 mL) was stirred overnight at 90°C. After concentration, the resulting mixture was purified by column chromatography, eluting with PE/EA = 10/1 to give target compound **12-2** as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 2H), 4.41 (s, 2H). LC-MS: m/z = 206.9 $[M+H]^+$.

[00363] Step 2: The same procedure with **step 6** of **Scheme 11** was applied to the preparation of compound **12-3** as yellow oil. LC-MS: m/z = 302.9 $[M+H]^+$.

[00364] Step 3: The same procedure with **step 1** of **Scheme 9** was applied to the preparation of compound **12-4** as yellow oil. LC-MS: m/z = 311.9 $[M+H]^+$.

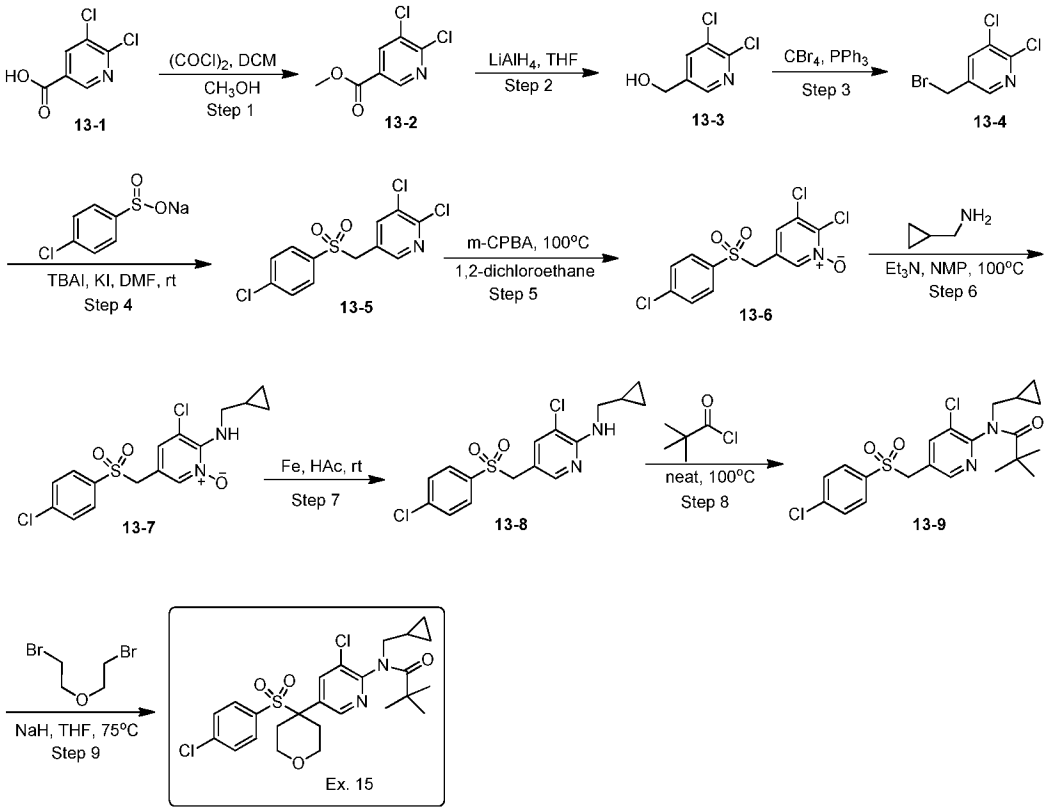
[00365] Step 4: The same procedure with **step 2** of **Scheme 11** was applied to the preparation of compound **12-5** as yellow oil. LC-MS: m/z = 396.1 $[M+H]^+$.

[00366] Example #9: The same procedure with **step 7** of **Scheme 11** was applied to the preparation of **Example #9** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 2H), 7.47 - 7.35 (m, 4H), 4.03 - 3.91 (m, 4H), 3.29 (t, *J* = 11.5 Hz, 2H), 2.63 - 2.34 (m, 4H), 1.28 - 1.16

(m, 12H). HPLC = 99.9% (214 nm), 99.8% (254 nm), t_R = 4.77 min. LC-MS: m/z = 466.0 $[M+H]^+$.

[00367] Example #2: was prepared following the procedure for **Example #9**, but oxybis(ethane-2,1-diyl)dimethanesulfonate was used in **step 5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 2H), 7.45 - 7.37 (m, 4H), 3.96 - 3.88 (m, 2H), 3.39 - 3.34 (m, 2H), 2.68 - 2.63 (m, 2H), 1.25 - 1.12 (m, 12H), 0.65 - 0.51 (m, 4H). HPLC = 98.7% (214 nm), 97.1% (254 nm), t_R = 5.42 min. LC-MS: m/z = 461.9 $[M+H]^+$.

[00368] Scheme 13. Synthesis of Examples #6, 8, 15, and 16.



[00369] Step 1: The same procedure with **step 1** of **Scheme 6** was applied to the preparation of compound **13-2**. LC-MS: m/z = 206.0 $[M+H]^+$.

[00370] Step 2: The same procedure with **step 3** of **Scheme 6** was applied to the preparation of compound **13-3**. LC-MS: m/z = 178.0 $[M+H]^+$.

[00371] Step 3: The same procedure with **step 4** of **Scheme 7**was applied to the preparation of compound **13-4**. LC-MS: m/z = 239.9 $[M+H]^+$.

[00372] Step 4: The same procedure with **step 5** of **Scheme 7** was applied to the preparation of compound **13-5**. LC-MS: m/z = 336.0 $[M+H]^+$.

[00373] **Step 5**: Compound **13-5** (0.8 g, 2.4 mmol) and m-CPBA (0.85 g, 4.8 mmol) was added into 1,2-dichloroethane (30 mL), the mixture was stirred for 12 hours at 100 °C, after removed of most of 1,2-dichloroethane, the residue was purified by flash column chromatography to give product **13-6** as a white solid. LC-MS: m/z = 351.9 $[M+H]^+$.

[00374] **Step 6**: A solution of cyclopropylmethanamine (150 mg, 1.55 mmol) and compound **13-6** (150 mg, 0.42 mmol) in NMP (10 mL) was stirred at 100 °C for 12 hours. After being concentrated, the crude product was purified by flash column chromatography to give product **13-7** as white solid. LC-MS: m/z = 387.0 $[M+H]^+$.

[00375] **Step 7**: A solution of compound **13-7** (110 mg, 0.28 mmol), iron power (56 mg, 0.84 mmol) in CH_3COOH (5 mL) was stirred at rt for 12 hours. After being concentrated, the crude product was purified by flash column chromatography to give product **13-8** as yellow solid. LC-MS: m/z = 370.9 $[M+H]^+$.

[00376] **Step 8**: Compound of **13-8** (80 mg, 0.22 mmol) was added pivaloyl chloride (5 mL), the mixture was stirred for 12 hours at 100 °C. After removed of most of pivaloyl chloride, water (10 mL) was added. The mixture was extracted with EtOAc (10 mL x 3). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the product **13-9** as yellow solid. LC-MS: m/z = 454.9 $[M+H]^+$.

[00377] **Example #15**: To a mixture of compound **13-9** (60 mg, 0.13 mmol) and NaH (11 mg, 0.26 mmol) in THF (10 mL) was added 1-(2-bromoethoxy)-2-bromoethane (46 mg, 0.2 mmol) at rt. The resulting mixture was stirred for 12 hours at 75°C, then quenched with H_2O (15 mL), extracted with EA (15 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated and purified by preparative TLC to give **Example #15** as a yellow solid. ^1H NMR (300 MHz, CDCl3) δ 8.05 - 7.40 (m, 6H), 4.04 - 3.22 (m, 6H), 2.64 - 2.34 (m, 4H), 1.13 - 1.03 (m, 10H), 0.37 - 0.01 (m, 4H). HPLC = 95.2% (214 nm), 95.8% (254 nm), t_R = 5.09 min. LC-MS: m/z = 524.9 $[M+H]^+$.

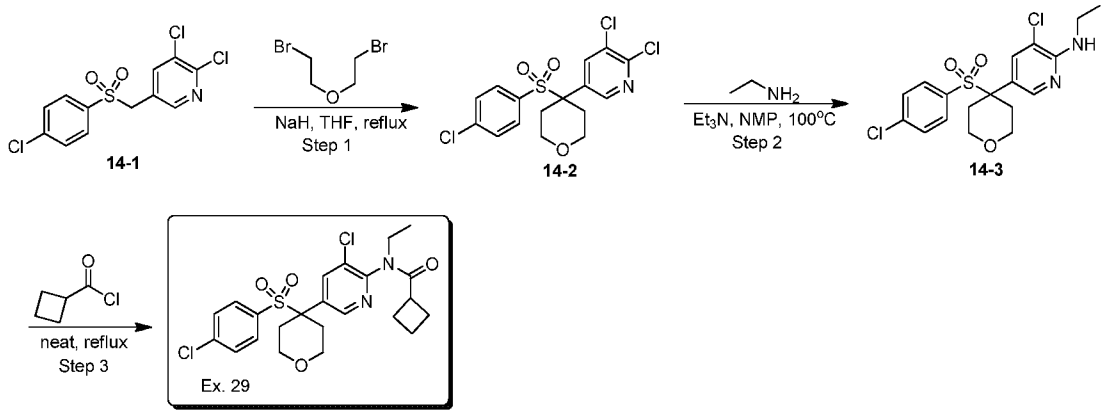
[00378] **Example #8:** was prepared following the procedure for **Example #15**, except cyclopropaneamine was used in **step 6**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 - 7.32 (m, 6H), 4.05 - 4.01 (m, 2H), 3.32 - 3.22 (m, 3H), 2.65 - 2.61 (m, 2H), 2.38 - 2.34 (m, 2H), 1.16 (s, 9H), 0.84 - 0.53 (m, 4H). HPLC = 98.3% (214 nm), 99.2% (254 nm), t_R = 4.67 min. LC-MS: m/z = 510.9 $[M+H]^+$.

[00379] **Example #6:** was prepared following the procedure for **Example #15**, except sodium 4-(trifluoromethyl)benzenesulfonate was used in **step 4**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 - 7.57 (m, 6H), 4.04 - 3.22 (m, 6H), 2.62 - 2.36 (m, 4H), 1.13 - 1.03 (m, 10H), 0.38 -

0.01 (m, 4H). HPLC = 95.1% (214 nm), 96.9% (254 nm), t_R = 5.20 min. LC-MS: m/z = 558.9 $[M+H]^+$.

[00380] Example #16: was prepared following the procedure for **Example #15**, except 2-methoxyethaneamine was used in **step 6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 - 7.35 (m, 6H), 4.18 - 3.21 (m, 11H), 2.74 - 2.28 (m, 4H), 1.12 (s, 9H). HPLC = 99.4% (214 nm), 99.4% (254 nm), t_R = 4.66 min. LC-MS: m/z = 528.9 $[M+H]^+$.

[00381] Scheme 14. Synthesis of Example #28 and #29



[00382] Step 1: To a mixture of compound **14-1** (1 g, 3 mmol) and NaH (240 mg, 6 mmol) in THF (40 mL) was added 1-(2-bromoethoxy)-2-bromoethane (1.05 g, 4.5 mmol) at rt. The resulting mixture was stirred for 4 hours at 75°C, then quenched with H_2O (50 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography to give product **14-2** as a yellow solid. LC-MS: m/z = 405.9 $[M+H]^+$.

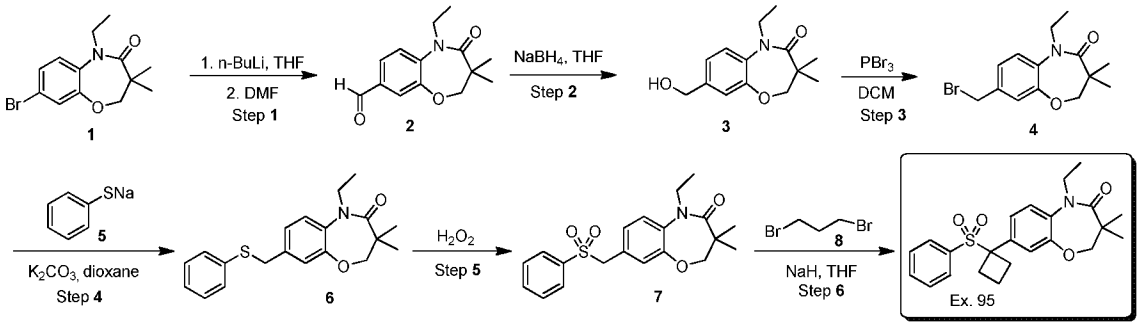
[00383] Step 2: A solution of $EtNH_2$ (110 mg, 2.45 mmol) and compound **14-3** (200 mg, 0.49 mmol) in NMP (15 mL) was stirred at 100 °C for 12 hours. After being concentrated, the crude product was purified by pre-TLC to give product **14-3** as a white solid. LC-MS: m/z = 415.0 $[M+H]^+$.

[00384] Example #29: Compound of **14-3** (70 mg, 0.168 mmol) was added cyclobutanecarbonyl chloride (2 mL), the mixture was stirred for 6 hours at 100 °C. After removed of most of cyclobutanecarbonyl chloride, water (10 mL) was added. The mixture was extracted with EtOAc (15 mL x 2). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated to the residue. The residue was purified by pre-HPLC to give the **Example #29** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 2.4 Hz, 1H), 7.80 (s, 1H), 7.47 - 7.39 (m, 4H), 4.03 (d, J = 12 Hz, 2H), 3.79 (br, 2H), 3.33 - 3.31 (m, 2H), 2.94

(br, 2H), 2.61 - 2.59 (m, 2H), 2.43 - 2.41 (m, 4H), 1.82 (br, 4H), 1.14 (t, J = 7.2 Hz, 3H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.46 min. LC-MS: m/z = 496.9 $[M+H]^+$.

[00385] Example #28: was prepared following the procedure for **Example #29**, except cyclopentanecarbonyl chloride was used in **step 3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 2.4 Hz, 1H), 7.81 (s, 1H), 7.40 - 7.32 (m, 4H), 4.03 (d, J = 11.4 Hz, 2H), 3.85 (br, 2H), 3.37 - 3.32 (m, 2H), 2.62 - 2.58 (m, 2H), 2.41 - 2.37 (m, 2H), 1.95 - 1.41 (m, 9H), 1.15 (t, J = 6.9 Hz, 3H). HPLC = 98.2% (214 nm), 99.8% (254 nm), t_R = 4.69 min. LC-MS: m/z = 510.9 $[M+H]^+$.

[00386] Scheme 15. Synthesis of Example #95.



[00387] Step 1: Under a nitrogen atmosphere, to a solution of compound **15-1** (6 g, 20.2 mmol) in dry THF (50 mL) was added n-Butyllithium, 2.5 M solution in THF (12 mL, 30.3 mmol) dropwise under minus 80 degree. The solution was stirred at -80 degree for 1 hr, followed by addition of dry DMF (2.9 g, 40.4 mmol). The mixture was stirred for another 1 hr at this temperature and then quenched with H_2O (20 mL), extracted with EA (20 mL X 3).The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product The crude product was purified by column chromatography, eluting with PE/EA = 4/1 to give compound **15-2** as a yellow oil. LC-MS: m/z = 248.2 $[M+H]^+$.

[00388] Step 2: A mixture of compound **15-2** (3.7 g, 15 mmol), $NaBH_4$ (1.7 g, 44.9 mmol) in dry THF (50 mL) was stirred at r.t overnight. After quenched with H_2O (20 mL), the mixture was extracted with EA (50 mL X 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography, eluting with PE/EA = 2/1, to give compound **15-3** as white solid. LC-MS: m/z = 250.2 $[M+H]^+$.

[00389] Step 3: To a solution of compound **15-3** (2.7 g, 10.8 mmol) in DCM (100 mL) was added PBr_3 (5.9 g, 21.7 mmol) at 0 degree. The mixture was stirred at 0 degree for 2 hrs and

then poured into ice water (100 mL). The mixture was basified with 1 N NaOH to pH = 7, extracted with DCM (100 mL X 3). The combined organic layer was washed brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1, to give compound **15-4** as yellow oil. LC-MS: m/z = 312.0 $[M+H]^+$.

[00390] **Step 4**: To a solution of compound **15-4** (0.8 g, 2.56 mmol) and K_2CO_3 (0.424 g, 3.07 mmol) in 1,4-dioxane (20 mL) was added sodium benzenethiolate (0.373 g, 2.82 mmol) at room temperature. The mixture was stirred at room temperature overnight. Then the mixture was poured into water (10 mL), extracted with DCM (20 mL X 3). The combined organic layer was washed brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **15-6a** as colorless oil. LC-MS: m/z = 342.1 $[M+H]^+$.

[00391] **Step 5**: To a solution of compound **15-6** (0.85 g, 2.49 mmol) in acetic acid (10 mL) was added 30% H_2O_2 (10 mL, 14.9 mmol) at room temperature. The mixture was stirred at room temperature for 2 hrs and then poured into ice water (100 mL). The mixture was extracted with DCM (20 mL X 3). The combined organic layer was washed brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 2/1, to give compound **15-7**. LC-MS: m/z = 374.2 $[M+H]^+$.

[00392] **Step 6**: A mixture of compound **7** (120 mg, 0.32 mmol), 1,3-dibromopropane **8** (195 mg, 0.97 mmol), NaH (39 mg, 60%, 1.61 mmol) in THF (20 mL) was stirred at 80 degree overnight. Then the mixture was diluted with H_2O (10 mL), extracted with EA (20 mL X 3). The combined organic layer was washed brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to give **Example #95** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 - 7.58 (m, 1H), 7.48 - 7.46 (m, 2H), 7.41 - 7.36 (m, 2H), 7.10 - 7.07 (m, 1H), 6.96 - 6.93 (m, 1H), 6.68 (d, *J* = 2.1 Hz, 1H), 4.12 (s, 2H), 3.92 (q, *J* = 7.2 Hz, 2H), 3.36 - 3.26 (m, 2H), 2.68 - 2.58 (m, 2H), 2.46 - 2.32 (m, 1H), 2.10 - 1.98 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 2H), 1.09 (s, 6H). LC-MS: m/z = 414.1 $[M+H]^+$.

[00393] The following **Examples (79, 80, 81, 82, 83, 84, 87, 88, 90, 91, 92, 93, 94, 96, 97, 98, and 99)** were all prepared following the same general procedure as outlined in **Scheme 15**. The procedures only differ by which aryl thiol was used in **step 4** and/or which dibromide was used in **step 6**.

[00394] **Example #96:** was prepared using 1,4-dibromobutane in **step 6**: ^1H NMR (300 MHz, CD_3OD) δ 7.65 - 7.60 (m, 1H), 7.45 - 7.38 (m, 4H), 7.19 - 7.08 (m, 2H), 6.92 (d, *J* = 2.1 Hz, 1H), 4.12 (s, 2H), 3.88 (q, *J* = 6.9 Hz, 2H), 2.83 - 2.75 (m, 2H), 2.38 - 2.30 (m, 2H),

2.07 - 1.95 (m, 2H), 1.72 - 1.68 (m, 2H), 1.14 (t, J = 6.9 Hz, 3H), 1.03 (s, 6H). HPLC = 98.5% (214 nm), 99.1% (254 nm), t_R = 4.72 min. LC-MS: m/z = 428.2 $[M+H]^+$.

[00395] Example #93: was prepared using 4-chlorobenzenethiol in **step 4**: white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 4H), 7.07 - 7.04 (m, 1H), 6.90 - 6.86 (m, 1H), 6.68 (d, J = 2.1 Hz, 1H), 4.09 (s, 2H), 3.87 (q, J = 7.2 Hz, 2H), 3.27 - 3.17 (m, 2H), 2.63 - 2.53 (m, 2H), 2.41 - 2.26 (m, 1H), 2.02 - 1.93 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 99.3% (214 nm), 100% (254 nm), t_R = 4.91 min. LC-MS: m/z = 448.1 $[M+H]^+$.

[00396] Example #98: was prepared using 4-chlorobenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, CD_3OD) δ 7.50 - 7.36 (m, 4H), 7.26 – 7.19 (m, 1H), 7.16 - 7.09 (m, 1H), 7.00 (d, J = 3.6 Hz, 1H), 4.15 (s, 2H), 3.90 (q, J = 6.9 Hz, 2H), 2.86 - 2.74 (m, 2H), 2.43 - 2.32 (m, 2H), 2.08 - 2.00 (m, 2H), 1.77 - 1.67 (m, 2H), 1.16 (t, J = 7.0 Hz, 3H), 1.04 (s, 6H). HPLC = 98.5% (214 nm), 99.3% (254 nm), t_R = 8.14 min. LC-MS: m/z = 402.1 $[M+H]^+$.

[00397] Example #91: was prepared using 4-chlorobenzenethiol in **step 4** and 1,5-dibromopentane in **step 6**:white solid, ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 - 7.35 (m, 4H), 7.28 - 7.25 (m, 1H), 7.16 - 7.12 (m, 1H), 7.02 (d, J = 2.4 Hz, 1H), 4.16 (s, 2H), 3.91 (q, J = 6.9 Hz, 2H), 2.62 - 2.58 (m, 2H), 2.24 - 2.14 (m, 2H), 1.79 - 1.75 (m, 2H), 1.64 - 1.60 (m, 1H), 1.38 - 1.15 (m, 6H), 1.04 (s, 6H). HPLC = 96.2% (214 nm), 97.3% (254 nm), t_R = 5.61 min.. LC-MS: m/z = 496.1 $[M+H]^+$.

[00398] Example #90: was prepared using 4-chlorobenzenethiol in **step 4** and 1-bromo-2-((2-bromothoxy)ethane in **step 6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.30 (m, 4H), 7.14 - 7.12 (m, 1H), 7.05 - 7.02 (m, 1H), 6.91 (d, J = 2.1 Hz, 1H), 4.14 (s, 2H), 3.98 - 3.86 (m, 4H), 3.30 (t, J = 11.4 Hz, 2H), 2.67 - 2.57 (m, 2H), 2.37 - 2.32 (m, 2H), 1.21 (t, J = 6.9 Hz, 3H), 1.06 (s, 6H). HPLC = 98.9% (214 nm), 100% (254 nm), t_R = 4.64 min. LC-MS: m/z = 478.1 $[M+H]^+$.

[00399] Example #94: was prepared using 4-(trifluoromethyl)benzenethiol in **step 4:** white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 - 7.55 (m, 4H), 7.07 - 7.04 (m, 1H), 6.92 - 6.89 (m, 1H), 6.65 (s, 1H), 4.05 (s, 2H), 3.87 (q, J = 6.9 Hz, 2H), 3.32 - 3.23 (m, 2H), 2.66 - 2.57 (m, 2H), 2.44 - 2.32 (m, 1H), 2.06 - 1.96 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.03 (s, 6H). HPLC = 99.1% (214 nm), 99.8% (254 nm), t_R = 5.37 min. LC-MS: m/z = 482.1 $[M+H]^+$.

[00400] Example #97: was prepared using 4-(trifluoromethyl)benzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, CD_3OD) δ 7.75 - 7.61 (m, 4H), 7.21 - 7.11 (m, 2H), 6.96 (d, J = 2.4 Hz, 1H), 4.10 (s, 1H), 3.88 (q, J = 6.9 Hz, 2H),

2.87 - 2.78 (m, 2H), 2.43 - 2.34 (m, 2H), 2.06 - 2.01 (m, 2H), 1.78 - 1.69 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 6H). HPLC = 96.2% (214 nm), 97.3% (254 nm), t_R = 5.61 min.. LC-MS: m/z = 496.1 $[M+H]^+$.

[00401] Example #92: was prepared using 4-(trifluoromethyl)benzenethiol in **step 4** and 1,5-dibromopentane in **step 6**: white solid, ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 - 7.74 (m, 2H), 7.62 - 7.59 (m, 2H), 7.27 - 7.25 (m, 1H), 7.18 - 7.14 (m, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 4.12 (s, 2H), 3.90 (q, *J* = 6.9 Hz, 2H), 2.65 - 2.61 (m, 2H), 2.27 - 2.17 (m, 2H), 1.81 - 1.75 (m, 2H), 1.67 - 1.60 (m, 1H), 1.40 - 1.15 (m, 6H), 1.03 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.78 min. LC-MS: m/z = 510.1 $[M+H]^+$.

[00402] Example #88: was prepared using 3,4-dichlorobenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**:white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 - 7.36 (m, 2H), 7.25 - 7.22 (m, 1H), 7.07 - 6.97 (m, 3H), 4.15 (s, 2H), 3.87 (q, *J* = 6.9 Hz, 2H), 2.80 - 2.72 (m, 2H), 2.32 - 2.23 (m, 2H), 2.09 - 1.98 (m, 2H), 1.73 - 1.68 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.79 min. LC-MS: m/z = 496.1 $[M+H]^+$.

[00403] Example #81: was prepared using 3,5-dimethylbenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.05 - 6.91 (m, 6H), 4.13 (s, 2H), 3.89 - 3.85 (m, 2H), 2.81 - 2.77 (m, 2H), 2.28 - 2.19 (m, 10H), 1.65 (brs, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 98.6% (214 nm), 99.3% (254 nm), t_R = 5.21 min.. LC-MS: m/z = 456.2 $[M+H]^+$.

[00404] Example #82: was prepared using 3,5-dichlorobenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.51 (s, 1H), 7.25 - 7.22 (m, 2H), 7.08 - 6.96 (m, 3H), 4.18 (s, 2H), 3.90 - 3.85 (m, 2H), 2.76 (brs, 2H), 2.30 (brs, 2H), 2.06 (brs, 2H), 1.71 (brs, 2H), 1.20 (t, *J* = 7.2, 3H), 1.05 (s, 6H). HPLC = 95.2% (214 nm), 95.9% (254 nm), t_R = 5.27 min. LC-MS: m/z = 496.1 $[M+H]^+$.

[00405] Example #84: was prepared using 4-ethylbenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.28 - 7.11 (m, 6H), 6.83 (s, 1H), 4.09 (s, 2H), 3.91 - 3.84 (m, 2H), 2.83 - 2.64 (m, 4H), 2.26 (brs, 2H), 2.03 (brs, 2H), 1.66 (brs, 2H), 1.25 - 1.18 (m, *4*H), 1.05 (s, 6H). HPLC = 97.5% (214 nm), 97.3% (254 nm), t_R = 5.53 min. LC-MS: m/z = 456.2 $[M+H]^+$.

[00406] Example #87: was prepared using 4-isopropylbenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, CD_3OD) *δ* 7.31 - 7.04 (m, 6H), 6.78 (s, 1H), 4.07 (s, 2H), 3.88 - 3.83 (m, 2H), 2.92 - 2.78 (m, 3H), 2.27 (brs, 2H), 2.02 (brs,

2H), 1.65 (brs, 2H), 1.23 - 1.14 (m, 9H), 1.04 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.56 min. LC-MS: m/z = 470.2 $[M+H]^+$.

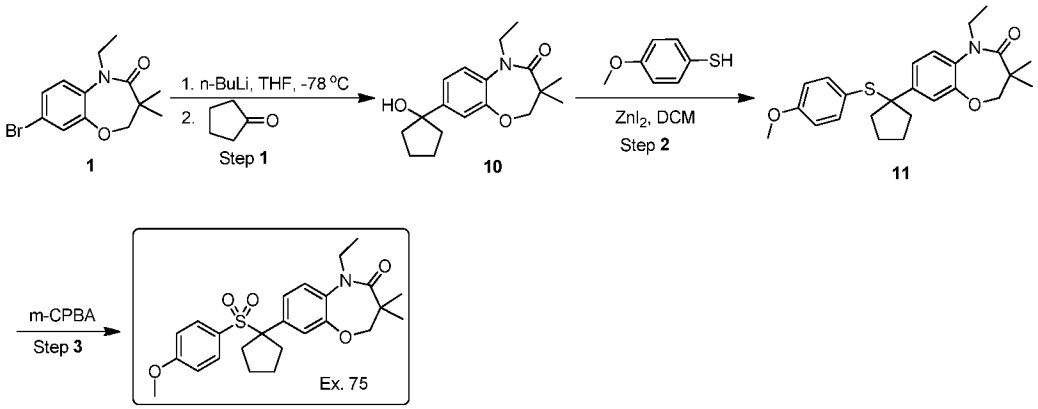
[00407] Example #83: was prepared using 3-(trifluoromethoxy)benzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.37 (m, 3H), 7.05 - 6.92 (s, 4H), 4.14 (s, 2H), 3.91 - 3.86 (m, 2H), 2.79 - 2.76 (m, 3H), 2.28 (brs, 2H), 2.05 (brs, 2H), 1.68 (brs, 2H), 1.18 (t, J = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 98.6% (214 nm), 98.7% (254 nm), t_R = 5.68 min. LC-MS: m/z = 512.2 $[M+H]^+$.

[00408] Example #79: was prepared using 3,4-dimethoxybenzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 - 6.71 (m, 6H), 4.11 (s, 2H), 3.88 - 3.71 (m, 8H), 2.77 - 2.75 (m, 3H), 2.26 (brs, 2H), 2.01 (brs, 2H), 1.64 (brs, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.05 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.59 min. LC-MS: m/z = 488.1 $[M+H]^+$.

[00409] Example #80: was prepared using 4-(*tert*-butyl)benzenethiol in **step 4** and 1,4-dibromobutane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.25 (m, 4H), 7.12 - 6.76 (m, 3H), 4.06 (s, 2H), 3.88 - 3.83 (m, 8H), 2.87 - 2.85 (m, 3H), 2.27 (brs, 2H), 2.03 (brs, 2H), 1.57 (brs, 2H), 1.29 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H), 1.05 (s, 6H).. HPLC = 98.8% (214 nm), 98.8% (254 nm), t_R = 5.78 min. LC-MS: m/z = 484.1 $[M+H]^+$.

[00410] Example #99: was prepared using 2 equivelents of iodomethane in **step 6**: white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, J = 7.2 Hz, 1H), 7.47 - 7.40 (m, 2H), 7.37 - 7.28 (m, 2H), 7.24 - 7.17 (m, 1H), 7.12 - 7.05 (m, 1H), 7.00 - 6.96 (m, 1H), 4.12 (s, 2H), 3.88 (q, J = 7.0 Hz, 2H), 1.80 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H), 1.04 (s, 6H). HPLC = 98.5% (214 nm), 99.3% (254 nm), t_R = 8.14 min. LC-MS: m/z = 402.1 $[M+H]^+$.

[00411] Scheme 16. Synthesis of Example #75.



[00412] **Step 1**: Under nitrogen atmosphere, to a solution of compound **1** (4 g, 13.5 mmol) in dry THF (20 mL) was added n-Butyllithium, 2.5 M solution (in THF 8.1 mL, 20.2 mmol) dropwise under minus 80 degrees. The solution was stirred at -80 degree for 1 hr, followed by addition of cyclopentanone (2.3 g, 26.9 mmol). The mixture was stirred for another 1 hr at this temperature and then quenched with H_2O (5 mL), extracted with EA (20 mL X 3).The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product The crude product was purified by column chromatography, eluting with PE/EA = 2/1 2.29 g, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.27 (m, 1H), 7.23 - 7.21 (m, 1H), 7.15 - 7.11 (m, 1H), 4.20 (s, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 2.01 - 1.92 (s, 6H), 1.89 - 1.81 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 6H). LC-MS: m/z = 304.2 $[M+H]^+$.

[00413] **Step 2**: To a mixture of compound **16-10** (80 mg, 0.26 mmol) and ZnI_2 (42 mg, 0.13 mmol) in dry DCM (5 mL) was added 4-methoxybenzenethiol (44 mg, 0.32 mmol) at r.t. The resulting mixture was stirred at r.t for 0.5 hr, then quenched with H_2O (5 mL), extracted with EA (10 mL X 3).The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give product. LC-MS: m/z = 426.2 $[M+H]^+$.

[00414] **Example #75:** A mixture of compound **16-11** (83 mg, 0.2 mmol) and m-CPBA (101 mg, 0.59 mmol) in DCM (5 mL) was stirred at r.t for 2 hrs. Then it was diluted with EA (20 mL), and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to give product, which was purified by preparative TLC or HPLC to give target compound as white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 - 7.30 (m, 2H), 7.21 - 7.19 (m, 1H), 7.12 - 7.09 (m, 1H), 6.96 - 6.90 (m, 3H), 4.15 (s, 2H), 3.93 - 3.85 (m, 5H), 2.80 - 2.72 (m, 2H), 2.38 - 2.30 (m, 2H), 2.06 - 1.95 (m, 2H), 1.76 - 1.62 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 7.88 min. LC-MS: m/z = 458.2 $[M+H]^+$.

[00415] The following **Examples (64. 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 77, 78, and 86)** where all prepared following the same general procedure as outlined in **Scheme 16**. The procedures only differ by which thiol was used in **step 2**.

[00416] **Example #74:** was prepared using 3-chloro-4-fluorobenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 - 7.48 (m, 1H), 7.40 - 7.31 (m, 2H), 7.24 - 7.21 (m, 1H), 7.09 - 7.06 (m, 2H), 4.19 (s, 2H), 3.90 (q, *J* = 6.9 Hz, 2H), 2.83 - 2.73 (m, 2H), 2.42 - 2.33(m, 2H), 2.11 - 1.98 (m, 2H), 1.74 - 1.65 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 6H). HPLC = 97.3% (214 nm), 100% (254 nm), t_R = 8.71 min. LC-MS: m/z = 480.0 $[M+H]^+$.

[00417] Example #70: was prepared using 3-(trifluoromethyl)benzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.98 - 7.96 (m, 1H), 7.70 - 7.62 (m, 2H), 7.49 (s, 1H), 4.17 (s, 2H), 3.89 - 3.87 (m, 2H), 2.80 - 2.77 (m, 2H), 2.39 - 2.37 (m, 2H), 2.07 - 2.05 (m, 2H), 1.73 - 1.71 (m, 2H), 1.20 - 1.15 (m, 3H), 1.01 (s, 6H). HPLC = 99.4% (214 nm), 99.5% (254 nm), t_R = 5.56 min. LC-MS: m/z = 496.3 $[M+H]^+$.

[00418] Example #73: was prepared using 4-methylbenzenethiol in **step 2**:: H NMR (300 MHz, CD_3OD) δ 7.30 - 7.18 (m, 5H), 7.11 - 7.08 (m, 1H), 6.94 (d, J = 2.4 Hz, 1H), 4.14 (s, 2H), 3.89 (q, J = 6.9 Hz, 2H), 2.83 - 2.73 (m, 2H), 2.40 - 2.29 (m, 5H), 2.04 - 1.99 (m, 2H), 1.72 - 1.67 (m, 2H), 1.15 (t, J = 7.2 Hz, 1H), 1.04 (s, 6H). HPLC = 99.0% (214 nm), 98.7% (254 nm), t_R = 8.32 min. LC-MS: m/z = 442.1 $[M+H]^+$.

[00419] Example #67: was prepared using 3,4-dimethylbenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 - 6.97 (m, 6H), 4.16 (s, 2H), 3.97 - 3.88 (m, 2H), 2.79 - 2.72 (m, 2H), 2.32 - 2.23 (m, 8H), 2.01 (brs, 2H), 1.69 (brs, 2H), 1.16 (t, J = 7.2 Hz, 3H), 1.03 (s, 6H). HPLC = 99.8% (214 nm), 99.8% (254 nm), t_R = 5.22 min. LC-MS: m/z = 456.2 $[M+H]^+$.

[00420] Example #66: was prepared using 4-cyanobenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.81 - 7.59 (m, 4H), 7.23 - 7.05 (m, 3H), 4.15 (s, 2H), 3.90 - 3.88 (m, 2H), 2.81 (brs, 2H), 2.39 (brs, 2H), 2.04 (brs, 2H), 1.71 (brs, 2H), 1.13 (t, J = 7.2 Hz, 3H), 0.97 (s, 6H). HPLC = 97.6% (214 nm), 98.6% (254 nm), t_R = 7.65 min. LC-MS: m/z = 453.1 $[M+H]^+$.

[00421] Example #78: was prepared using 4-(trifluoromethoxy)benzenethiol in **step 2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 - 7.43 (m, 2H), 7.25 - 6.86 (m, 5H), 4.10 (s, 2H), 3.88 - 3.83 (m, 2H), 2.80 (brs, 2H), 2.28 (brs, 2H), 2.05 (brs, 2H), 1.68 (brs, 2H), 1.17 (t, J = 7.2 Hz, 3H), 1.04 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.46 min. LC-MS: m/z = 512.0 $[M+H]^+$.

[00422] Example #65: was prepared using 3-(trifluoromethoxy)-4-chlorobenzenethiol in **step 2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.48 (s, 1H), 7.26 - 7.05 (m, 3H), 4.17 (s, 2H), 3.89 - 3.87 (m, 2H), 2.78 (brs, 2H), 2.38 (brs, 2H), 2.05 (brs, 2H), 1.73 (brs, 2H), 1.18 (t, J = 7.2 Hz, 3H), 1.00 (s, 6H). HPLC = 96.4% (214 nm), 96.4% (254 nm), t_R = 5.89 min. LC-MS: m/z = 580.1 $[M+H]^+$.

[00423] Example #69: was prepared using 3- fluoro-4-methoxybenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.32 - 6.89 (m, 6H), 4.16 (s, 2H), 3.94 - 3.91 (m, 5H), 2.75 (brs, 2H), 2.35 (brs, 2H), 2.02 (brs, 2H), 1.89 (brs, 2H), 1.15 (t, J = 6.9 Hz, 3H), 1.03 (s, 6H). HPLC = 99.2% (214 nm), 99.6% (254 nm), t_R = 5.11 min. LC-MS: m/z = 476.1 $[M+H]^+$.

[00424] Example #86: was prepared using 3-chloro-5-fluorobenzenethiol in **step 2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 - 7.26 (m, 1H), 7.19 (s, 1H), 7.09 - 6.96 (m, 4H), 4.16 (s, 2H), 3.90 - 3.85 (m, 2H), 2.78 - 2.75 (m, 2H), 2.33 - 2.30 (m, 2H), 2.08 - 2.04 (m, 2H), 1.72 - 1.70 (m, 2H), 1.21 - 1.17 (m, 3H), 1.06 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.36 min. LC-MS: m/z = 480.1 $[M+H]^+$.

[00425] Example #72: was prepared using 3-isopropoxybenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 - 7.31 (m, 1H), 7.22 - 7.13 (m, 3H), 6.81 - 6.80 (m, 1H), 4.54 - 4.52 (m, 1H), 4.15 (s, 1H), 3.90 - 3.88 (m, 2H), 2.78 - 2.77 (m, 2H), 2.38 - 2.36 (m, 2H), 2.02 - 1.99 (m, 2H), 1.70 - 1.68 (m, 2H), 1.29 - 1.27 (m, 6H), 1.19 - 1.15 (m, 3H), 1.03 (s, 6H). HPLC = 95.6% (214 nm), 97.7% (254 nm), t_R = 5.39 min. LC-MS: m/z = 486.2 $[M+H]^+$.

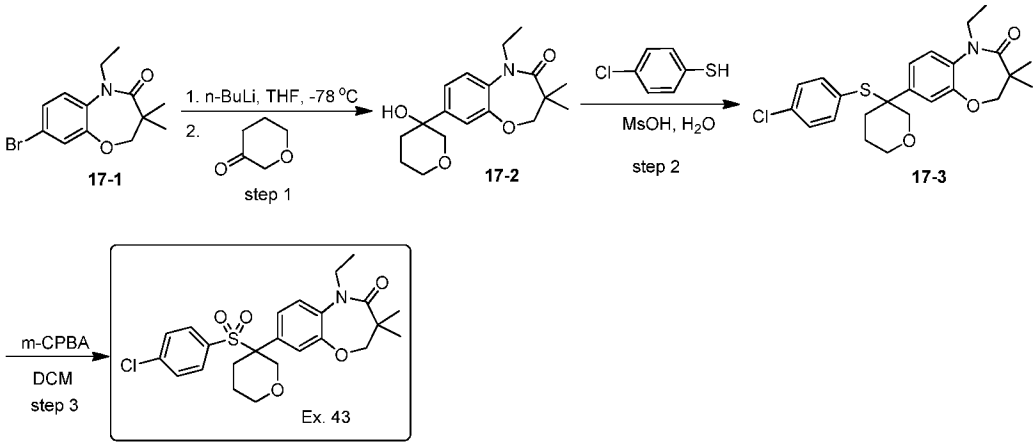
[00426] Example #68: was prepared using 3,5-difluorobenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.33 - 7.01 (m, 6H), 4.17 (s, 2H), 3.91 - 3.88 (m, 2H), 2.80 (brs, 2H), 2.41 (brs, 2H), 2.09 (brs, 2H), 1.73 (brs, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.02 (s, 6H). HPLC = 96.2% (214 nm), 98.6% (254 nm), t_R = 5.35 min. LC-MS: m/z = 464.1 $[M+H]^+$.

[00427] Example #71: was prepared using 4-fluoro-3-methylbenzenethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.27 - 7.19 (m, 3H), 7.12 - 7.01 (m, 3H), 4.17 (s, 2H), 3.91 - 3.89 (m, 2H), 2.77 - 2.75 (m, 2H), 2.36 - 2.33 (m, 2H), 2.22 - 2.21 (m, 2H), 2.03 - 2.01 (m, 2H), 1.71 - 1.69 (m, 2H), 1.19 - 1.14 (m, 3H), 1.03 (s, 6H). HPLC = 95.1% (214 nm), 98.2% (254 nm), t_R = 5.37 min. LC-MS: m/z = 460.2 $[M+H]^+$.

[00428] Example #77: was prepared using cyclohexanethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.59 - 7.37 (m, 3H), 4.25 (s, 2H), 3.94 - 3.90 (m, 2H), 2.84 - 2.48 (m, 6H), 1.94 (brs, 2H), 1.78 - 1.34 (m, 7H), 1.30 - 1.03 (m, 14H). HPLC = 98.4% (214 nm), 98.6% (254 nm), t_R = 6.78 min. LC-MS: m/z = 434.2 $[M+H]^+$.

[00429] Example #64: was prepared using cyclopentanethiol in **step 2**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.55 - 7.35 (m, 3H), 4.42 (s, 2H), 3.95 - 3.91 (m, 2H), 3.31 - 3.29 (m, 1H), 2.65 (brs, 2H), 2.47 (brs, 2H), 1.94 (brs, 2H), 1.70 - 1.49 (m, 10H), 1.16 (t, J = 7.2 Hz, 3H), 1.01 (s, 6H). HPLC = 96.6% (214 nm), 97.8% (254 nm), t_R = 6.24 min. LC-MS: m/z = 420.2 $[M+H]^+$.

[00430] Scheme 17. Synthesis of Examples #43 and #76.



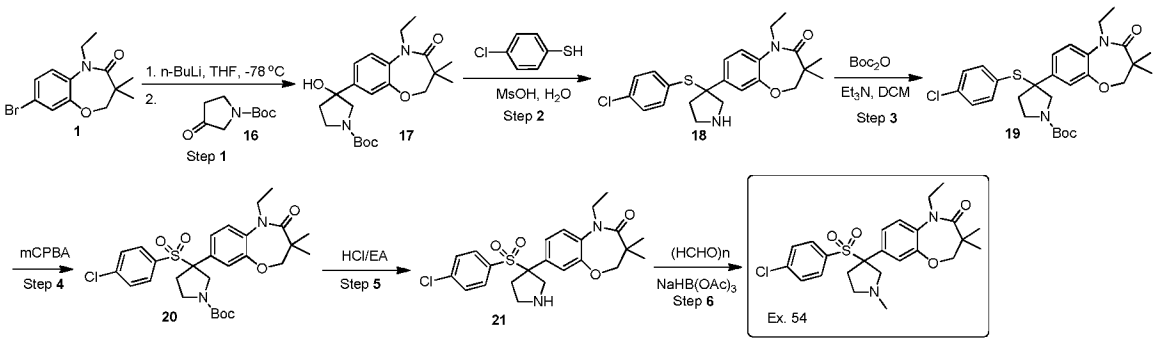
[00431] Step 1: Compound **17-2** was prepared from compound **17-1** using the procedure described in **Scheme 16, Step 1** using dihydro-2*H*-pyran-3(4H)-one instead of cyclopentanone. LC-MS: m/z = 320.2 $[M+H]^+$.

[00432] Step 2: Compound **17-3** was prepared from compound **17-2** using the procedure described in **Scheme 16, Step 2** using 4-chlorobenzenethiol in place of 4-methoxybenzenethiol. LC-MS: m/z = 446.1 $[M+H]^+$.

[00433] Example #43: Example # 43 was prepared from compound **17-3** using the procedure described in Scheme 16, step-3 using m-CPBA. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.29 (m, 4H), 7.17 - 7.09 (m, 2H), 7.07 (d, *J* = 1.8 Hz, 1H), 4.48 - 4.44 (m, 1H), 4.17 - 4.11 (m, 3H), 3.92 - 3.82 (m, 1H), 3.55 - 3.47 (m, 1H), 2.67 - 2.51 (m, 2H), 1.72 - 1.64 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 6H). HPLC = 99.9% (214 nm), 99.9% (254 nm), t_R = 4.72 min. LC-MS: m/z = 478.1 $[M+H]^+$.

[00434] Example #76: was prepared following **Scheme 17** except dihydrofuran-3(2H)-one was used in **step 1** and 4-(trifluoromethyl)benzenethiol was used in step 2: ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 - 7.70 (m, 4H), 7.25 - 7.22 (m, 1H), 7.06 - 7.03 (m, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 4.97 - 4.94 (m, 1H), 4.21 - 4.03 (m, 4H), 3.94 - 3.84 (m, 3H), 3.19 - 3.10 (m, 1H), 2.69 - 2.59 (m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 2.4 Hz, 6H). HPLC = 98.4% (214 nm), 98.9% (254 nm), t_R = 7.40 min. LC-MS: m/z = 498.1 $[M+H]^+$.

[00435] Scheme 18. Synthesis of Examples #54 and #56.



[00436] Step 1: Under nitrogen atmosphere, to a solution of compound **1** (1.68 g, 5.66 mmol) in dry THF (30 mL) was added n-Butyllithium, 2.5 M solution (in THF 3.4 mL, 8.48 mmol) dropwise under -78 degrees. The solution was stirred at -78 degree for 1 hr, followed by addition of tert-butyl 3-oxopyrrolidine-1-carboxylate (2.1 g, 11.3 mmol). The mixture was stirred for another 1 hr at this temperature and then quenched with H_2O (5 mL), extracted with EA (30 mL X 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product. The crude product was purified by column chromatography, eluting with PE/EA = 2/1, to give the product **16-17** as colorless oil. LC-MS: m/z = 405.1 $[M+H]^+$.

[00437] Step 2: To a mixture of compound **18-17** (1.2 g, 2.97 mmol) in MsOH (10 mL) and DCM (2 mL) was added 4-chlorobenzenethiol (1.3 g, 8.91 mmol) at r.t and followed by addition of H_2O (1 mL). The resulting mixture was stirred at r.t for 48 hrs. Then the mixture was diluted with H_2O (15 mL), extracted with EA (10 mL X 3).The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give crude product as a yellow oil. LC-MS: m/z = 431.0 $[M+H]^+$.

[00438] Step 3: To a mixture of compound **18-18** (0.65 g, 1.51 mmol) and TEA (0.46 g, 4.53 mmol) in DCM (20 mL) was added Boc_2O (0.49 g, 2.27 mmol). After being stirred at r.t for 2 hrs, the mixture was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 3/1, to give the product **18-19** as yellow oil. LC-MS: m/z = 531.0 $[M+H]^+$.

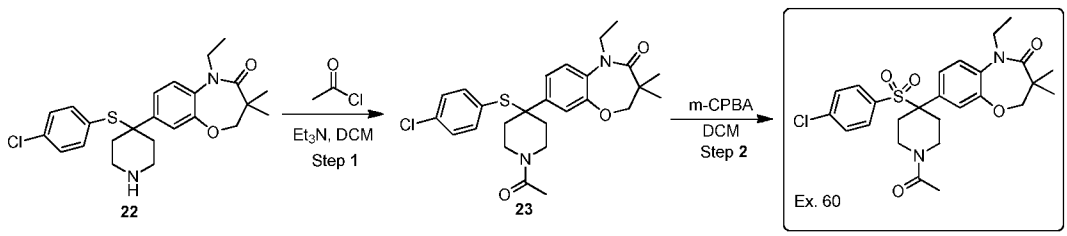
[00439] Step 4: To a mixture of compound **18-19** (0.3 g, 0.56 mmol) in DCM (20 mL) was added m-CPBA (0.48 g, 2.82 mmol). After being stirred at r.t for 2 hrs, the mixture was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 3/1, to give the product **18-20** as yellow oil. LC-MS: m/z = 585.1 $[M+Na]^+$.

[00440] Step 5: To a mixture of compound **18-20** (0.14 g, 0.25 mmol) in EA (5 mL) was added a sat. solution of HCl (g) in EA (5 mL) at 0 degree. After being stirred at 0 degree for 1 h, the mixture was concentrated and the residue was diluted with 0.5 N hydrochloric acid (10 mL). The solution was washed with EA (10 mL). Then it was basified with sat. $NaHCO_3$ solution to pH = 8~9 and extracted with EA (10 mL X 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give product. **18-21** as yellow oil. LC-MS: m/z = 463.1 $[M+H]^+$.

[00441] Example #54: A mixture of compound **18-21** (140 mg, 0.3 mmol), $(HCHO)_n$ (91 mg, 3.03 mmol) and a drop of HCOOH in DCM (10 mL) was stirred at r.t for 4 hrs, followed by the addition of $NaBH(OAc)_3$ (0.19 g, 0.9 mmol). After being stirred overnight, the mixture was diluted with DCM (20 mL). Then it was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give product, which was purified by preparative TLC and HPLC to give target compound as white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.48 - 7.40 (m, 4H), 7.24 - 7.21 (m, 1H), 7.10 - 7.06 (m, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.15 (s, 2H), 3.89 (q, *J* = 7.2 Hz, 2H), 3.63 - 3.59 (m, 1H), 3.47 - 3.43 (m, 1H), 3.06 - 2.98 (m, 1H), 2.85 - 2.81 (m, 2H), 2.61 - 2.52 (m, 1H), 2.41 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 6H). HPLC = 97.2% (214 nm), 100% (254 nm), t_R = 3.14 min. LC-MS: m/z = 477.2 $[M+H]^+$.

[00442] Example # 56: was prepared as described in **Scheme 18**, except *tert*-butyl 4-oxopiperidine-1-carboxylate was used in **step 1** instead of *tert*-butyl-3-oxopyrrolidine-1-carboxylate**:** ^1H NMR (300 MHz, CD_3OD) δ 7.50 - 7.40 (m, 4H), 7.30 - 7.28 (m, 1H), 7.18 - 7.14 (m, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 4.17 (s, 2H), 3.92 (q, *J* = 6.9 Hz, 2H), 2.93 - 2.89 (m, 2H), 2.65 - 2.51 (m, 4H), 2.17 (s, 3H), 1.99 - 1.91 (m, 2H), 1.19 (t, *J* = 6.9 Hz, 3H), 1.05 (s, 6H). HPLC = 98.8% (214 nm), 99.4% (254 nm), t_R = 3.39 min. LC-MS: m/z = 491.1 $[M+H]^+$.

[00443] Scheme 18b. Synthesis of Examples #59 and #60.



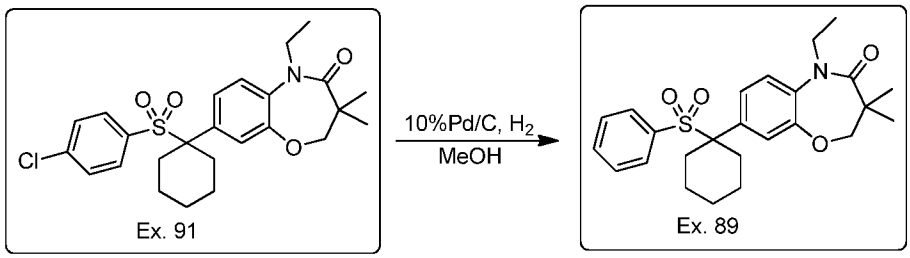
[00444] Step 1: To a mixture of compound **18b-22**, prepared on route to **Example #56,** (0.3 g, 0.68 mmol) and TEA (0.2 g, 2.03 mmol) in DCM (20 mL) was added acetyl chloride (0.08 g, 1.01 mmol) dropwise at 0 degree. After being stirred at r.t for 3 hrs, the mixture was

washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to give target compound as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 - 7.06 (m, 3H), 7.03 - 6.97 (m, 1H), 6.96 - 6.88 (m, 3H), 4.18 - 4.07 (m, 2H), 4.00 - 3.70 (m, 4H), 2.22 - 2.06 (m, 7H), 2.04 (s, 1H), 1.26 (t, *J* = 7.1 Hz, 1H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.04 (s, 6H). LC-MS: m/z = 508.9 $[M+H]^+$.

[00445] Example #60: was prepared from compound **18b-23** following the same procedure described for compound **18-20**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.49 - 7.37 (m, 4H), 7.32 - 7.29 (m, 1H), 7.20 - 7.16 (m, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 4.59 - 4.54 (m, 1H), 4.16 (s, 2H), 4.02 - 3.87 (m, 3H), 3.03 - 2.95 (m, 1H), 2.70 - 2.25 (m, 5H), 2.10 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 6H). HPLC = 96.5% (214 nm), 99.1% (254 nm), t_R = 4.04 min. LC-MS: m/z = 518.9 $[M+H]^+$.

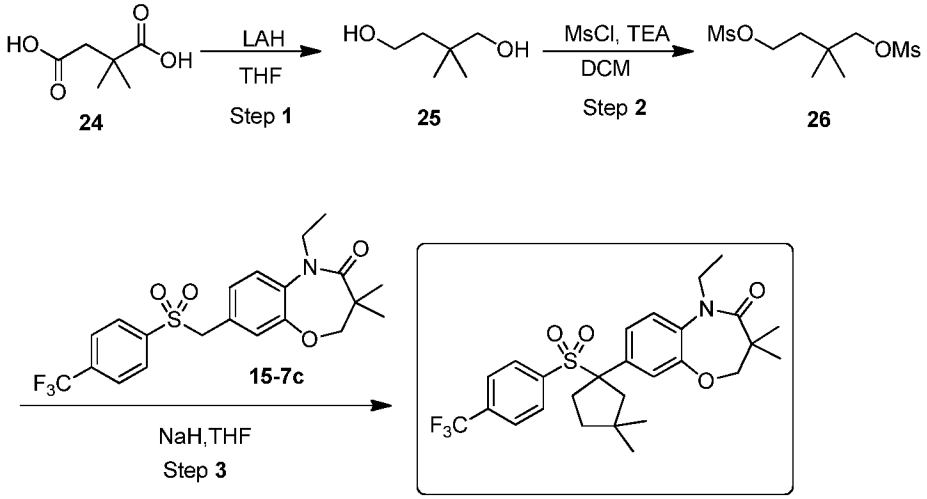
[00446] Example #59: was prepared as described in **Scheme 18b:** ^{1}H NMR (300 MHz, CD_3OD) δ 7.51 - 7.44 (m, 4H), 7.26 - 7.23 (m, 1H), 7.07 - 6.89 (m, 2H), 4.81 - 4.75 (m, 1H), 4.15 (s, 2H), 3.94 - 3.54 (m, 5H), 3.26 - 3.08 (m, 1H), 2.77 - 2.56 (m, 1H), 2.19 (s, 1H), 2.05 (s, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 6H). HPLC = 95.1% (214 nm), 95.9% (254 nm), t_R = 4.02 min. LC-MS: m/z = 504.9 $[M+H]^+$.

[00447] Scheme 19. Synthesis of Example #89.



[00448] Example #89: To a solution of **Example #91** (30 mg, 0.063 mmol) in MeOH (10 mL) was added 10%Pd/C (10 mg). The mixture was charged with hydrogen balloon and stirred at room temperature for 2 hrs. After filtration, the filtrate was concentrated to give the product as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.64 - 7.58 (m, 1H), 7.42 - 7.33 (m, 4H), 7.21 - 7.19 (m, 1H), 7.10 - 7.06 (m, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 4.10 (s, 2H), 3.86 (q, *J* = 6.9 Hz, 2H), 2.58 - 2.53 (m, 2H), 2.20 - 2.11 (m, 2H), 1.76 - 1.69 (m, 2H), 1.61 - 1.55 (m, 1H), 1.34 - 1.11 (m, 6H), 1.01 (s, 6H). HPLC = 98.1% (214 nm), 97.9% (254 nm), t_R = 4.95 min. LC-MS: m/z = 442.2 $[M+H]^+$.

[00449] Scheme 20. Synthesis of Example #63.



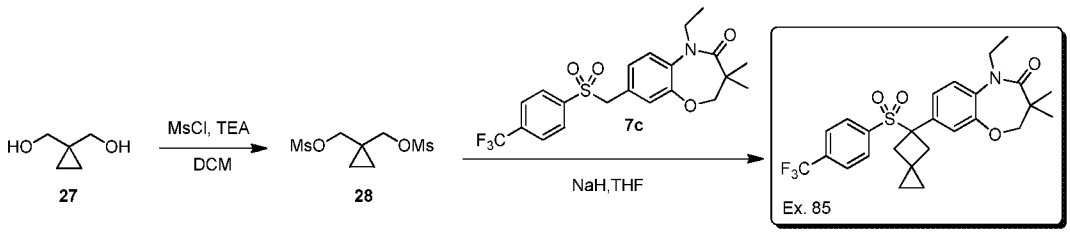
Ex. 63

[00450] Step 1: To a solution of compound **20-24** (0.5 g, 3.4 mmol) in THF (20 mL) was added LAH (0.39 g, 10.2 mmol) at 0 degree. The mixture was stirred at r.t for 4 hrs and then quenched with ice water (1 mL). The mixture was filtered and concentrated to give product as a yellow oil.

[00451] Step 2: To a solution of compound **20-25** (0.25 g, 2.2 mmol) and TEA (1.1 g, 11 mmol) in DCM (10 mL) was added methanesulfonyl chloride (0.75 g, 6.6 mmol) at 0 degree. The mixture was stirred at r.t for 3 hrs and then poured into ice water (10 mL). The mixture was extracted with DCM (10 mL X2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give product as a yellow oil. LC-MS: m/z = 274.7 $[M+H]^+$.

[00452] Example #63: To a solution of compound **15-7c** (70 mg, 0.16 mmol) and NaH (24 mg, 60% purity, 0.48 mmol) in THF (5 mL) was added compound **26** (110 mg, 0.45 mmol) at r.t. The mixture was stirred at 70 degree for 12 hrs and then poured into ice water (10 mL). The mixture was extracted with EA (10 mL X2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give crude product which was purified by preparative TLC to give target compound as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.75 - 7.72 (m, 2H), 7.61 - 7.58 (m, 2H), 7.20 - 7.16 (m, 2H), 7.97 - 7.96 (m, 1H), 4.12 - 4.10 (m, 2H), 3.89 - 3.87 (m, 2H), 2.92 - 2.90 (m, 1H), 2.73 - 2.71 (m, 1H), 2.55 - 2.50 (m, 1H), 2.42 - 2.39 (m, 1H), 1.93 - 1.91 (m, 1H), 1.54 - 1.51 (m, 1H), 1.24 (s, 3H), 1.17 - 1.12 (m, 3H), 1.02 - 1.01 (m, 6H), 0.83 (s, 3H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 6.04 min. LC-MS: m/z = 524.0 $[M+H]^+$.

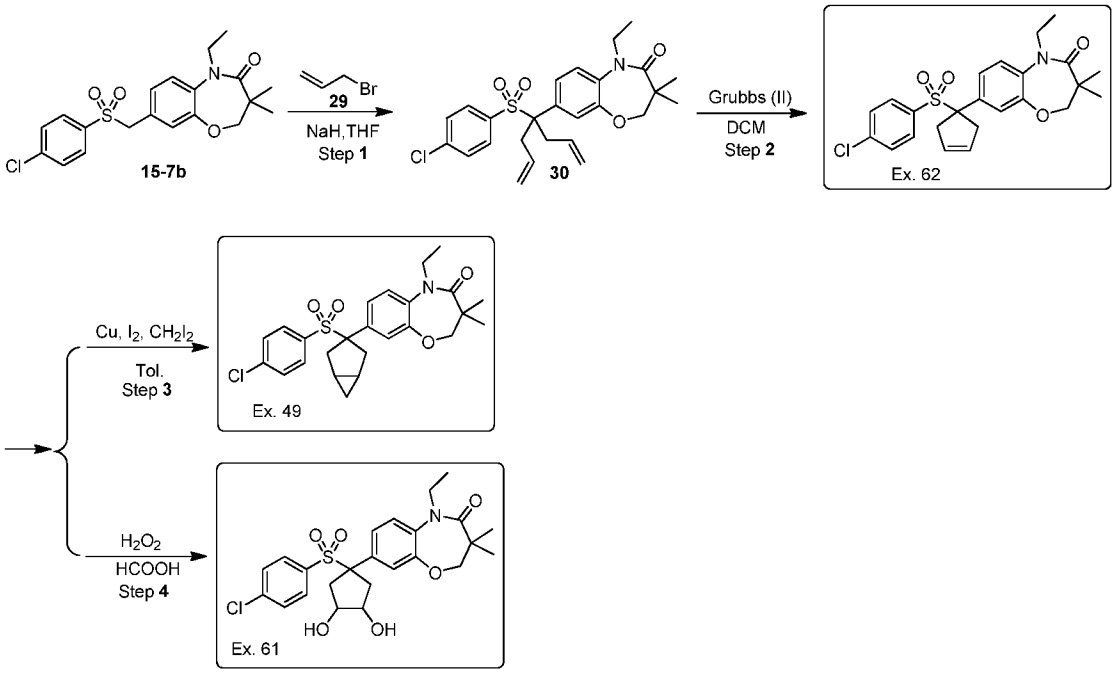
[00453] Scheme 20b. Synthesis of Example #85.



[00454] Compound 28: Was prepared from compound **20b-27** following the same procedure described for compound **20-26**. LC-MS: m/z = 258.7 $[M+H]^+$.

[00455] Example #85: Was prepared from compound **20b-28** following the same procedure described for **Example #63**. ^1H NMR (300 MHz, CD_3OD) δ 7.81 - 7.73 (m, 4H), 7.24 - 7.22 (m, 1H), 7.05 - 7.02 (m, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 4.09 (s, 2H), 3.89 (q, *J* = 7.2 Hz, 2H), 3.40 - 3.36 (m, 2H), 2.80 - 2.75 (m, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 6H), 0.63 - 0.58 (m, 2H), 0.51 - 0.46 (m, 2H). HPLC = 96.9% (214 nm), 98.5% (254 nm), t_R = 5.42 min. LC-MS: m/z = 508.1 $[M+H]^+$.

[00456] Scheme 21. Synthesis of Examples #49, 61 and 62.



[00457] Step 1: To a solution of compound **15-7b** (2.4 g, 5.9 mmol) in THF (60 mL) was added NaH (0.7 g, 29.5 mmol) in portions at r.t. After being stirred at r.t for 0.5 hrs, the mixture was added 3-bromoprop-1-ene (1.4 g, 11.8 mmol) and stirred overnight at 30 degree. Then it was poured into ice water (50 mL). The mixture was extracted with EA (60 mL X3).

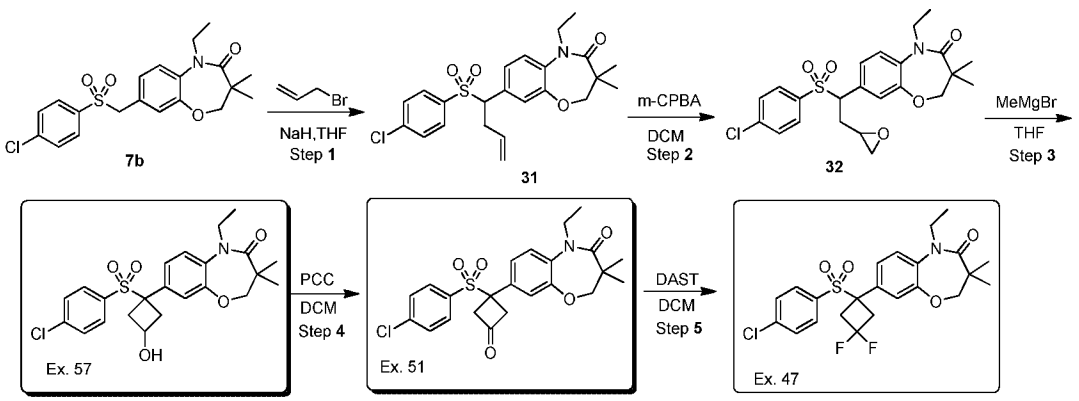
The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give product **30** as a yellow oil. LC-MS: m/z = 488.1 $[M+H]^+$.

[00458] Example #62: A solution of compound **21-30** (0.4 g, 0.82 mmol) and Grubbs Catalyst 2nd Generation (70 mg, 0.082 mmol) in DCM (10 mL) was stirred at r.t overnight. Then it was concentrated and the residue was purified by preparative TLC to give the product **Example # 62** as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.56 - 7.46 (m, 4H), 7.25 - 7.05 (m, 3H), 5.62 (s, 2H), 4.18 (s, 2H), 4.03 - 3.91 (m, 2H), 3.65 - 3.58 (m, 2H), 3.13 - 3.05 (m, 2H), 1.16 (t, J = 6.9 Hz, 3H), 1.03 (s, 6H). HPLC = 99.8% (214 nm), 99.8% (254 nm), t_R = 5.34 min. LC-MS: m/z = 460.1 $[M+H]^+$.

[00459] Example #49: To a solution of **Example #62** (100 mg, 0.22 mmol), Cu (0.5 g, 7.8 mmol), I_2 (50 mg, 0.2 mmol) in Toluene (10 mL) was added diiodomethane (0.64 mL, 7.8 mmol) at r.t. The mixture was stirred at 97 degree for 48 hrs and then filtered. The filtrate was concentrated to give crude product which was purified by preparative TLC to give target compound as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.50 - 6.98 (m, 7H), 4.17 (s, 2H), 3.93 - 3.91 (m, 2H), 3.36 - 3.34 (m, 1.5H), 2.77 - 2.75 (m, 0.5H), 2.61 - 2.53 (m, 2H), 1.55 - 1.52 (m, 1.5H), 1.18 (t, J = 7.2 Hz, 3H), 1.05 (s, 6H), 0.98 (brs, 0.5H), 0.44 (brs, 0.5H), 0.13 (brs, 0.5H). HPLC = 99.7% (214 nm), 99.8% (254 nm), t_R = 5.26 min. LC-MS: m/z = 474.1 $[M+H]^+$.

[00460] Example #61: A solution of **Example #62** (0.1 g, 0.22 mmol) in H_2O_2 (2 mL) and HCOOH (4 mL) was stirred at 40 degree for 3 hrs and then concentrated. The residue was purified by preparative TLC to give target compound as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.45 - 6.95 (m, 7H), 4.27 - 4.24 (m, 1H), 4.14 (s, 2H), 3.90 - 3.87 (m, 3H), 3.08 (brs, 2H), 2.77 - 2.73 (m, 2H), 2.27 - 2.19 (m, 1H), 1.15 (t, J = 6.9 Hz, 3H), 1.01 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 3.69 min. LC-MS: m/z = 493.9 $[M+H]^+$.

[00461] Scheme 22. Synthesis of Examples #47, 51 and 57.



[00462] **Step 1**: To a solution of compound **15-7b** (2.4 g, 5.9 mmol) in THF (60 mL) was added NaH (0.7 g, 29.5 mmol) in portions at r.t. After being stirred at r.t for 0.5 hrs, the mixture was added 3-bromoprop-1-ene (1.4 g, 11.8 mmol) and stirred overnight at 30 degree. Then it was poured into ice water (50 mL). The mixture was extracted with EA (60 mL X 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give the desired product as a yellow oil. LC-MS: m/z = 448.1 $[M+H]^+$.

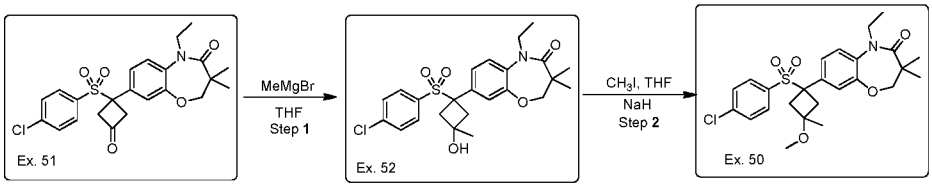
[00463] **Step 2**: To a solution of compound **22-31** (1.2 g, 2.68 mmol) in DCM (40 mL) was added m-CPBA (2.3 g, 13.4 mmol) at r.t. The mixture was stirred at r.t overnight and then washed with Na_2SO_3 (40 mL), brine (40 mL), dried over Na_2SO_4 and concentrated to give the product as a yellow solid. LC-MS: m/z = 464.1 $[M+H]^+$.

[00464] **Example #57**: To a solution of compound **22-32** (0.4 g, 0.86 mmol) in THF (20 mL) was added Methylmagnesiumbromide (3M in THF, 0.6 mL, 1.8 mmol) at minus 70 degree. The mixture was allowed to warm to r.t during 0.5 hrs. Then it was quenched with H_2O (30 mL) and extracted with EA (20 mL X 3). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated to give crude product. The crude product was purified by column chromatography, eluting with PE/EA = 3/1, to give pure product as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.48 - 7.37 (m, 4H), 7.23 - 7.07 (m, 2H), 6.86 (s, 1H), 4.11 (s, 2H), 4.10 - 3.84 (s, 3H), 3.08 - 3.05 (m, 2H), 2.96 - 2.93 (m, 2H), 1.13 (t, J = 6.9 Hz, 3H), 1.00 (s, 6H). HPLC = 97.5% (214 nm), 98.8% (254 nm), t_R = 4.02 min. LC-MS: m/z = 464.2 $[M+H]^+$.

[00465] **Example #51**: To a solution of **Example #57** (0.25 g, 0.54 mmol) in DCM (10 mL) was added PCC (0.1 g, 1.2 mmol) at r.t. The mixture was stirred at 30 degree for 5 hrs and then filtered. The filtrate was concentrated to give the product as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.49 - 7.46 (m, 4H), 7.26 - 7.01 (m, 2H), 6.86 (s, 1H), 4.18 - 4.11 (s, 4H), 3.91 - 3.88 (m, 4H), 1.14 (t, J = 7.2 Hz, 3H), 1.01 (s, 6H). HPLC = 98.4% (214 nm), 99.2% (254 nm), t_R = 4.51 min. LC-MS: m/z = 462.1 $[M+H]^+$.

[00466] **Example #47**: To a solution of **Example #51** (60 mg, 0.13 mmol) in DCM (10 mL) was added DAST (200 mg, 1.24 mmol) at r.t. After stirred at r.t for 48 hrs, the mixture was concentrated to give crude product which was purified by preparative TLC to give the target compound as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.50 - 7.13 (m, 6H), 6.85 (s, 1H), 4.12 (s, 2H), 3.89 - 3.28 (m, 4H), 3.26 - 3.24 (m, 2H), 1.14 (t, J = 6.9 Hz, 3H), 1.01 (s, 6H). HPLC = 98.1% (214 nm), 97.4% (254 nm), t_R = 4.98 min. LC-MS: m/z = 484.1 $[M+H]^+$.

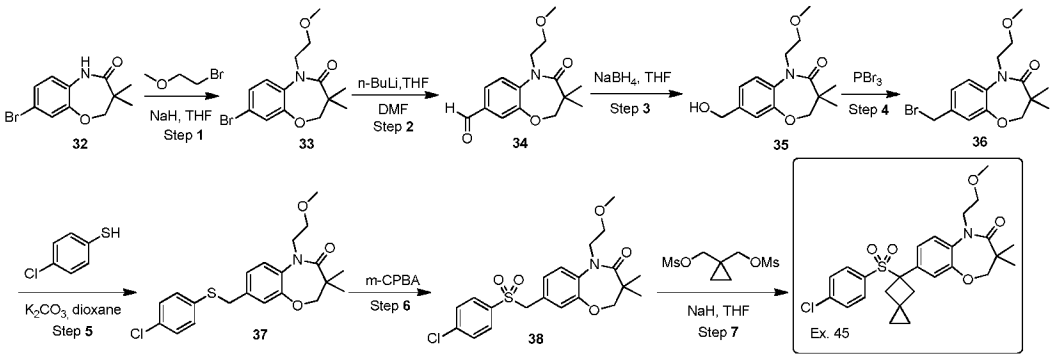
[00467] Scheme 22b. Synthesis of Examples #50 and #52.



[00468] Example #52: To a solution of **Example #51** (0.01 g, 0.02 mmol) in Et_2O (10 mL) was added Methylmagnesiumbromide (3M in THF, 0.2 mL, 0.6 mmol) at minus 70 degree. The mixture was allowed to warm to r.t and stirred overnight. Then it was concentrated to give crude product. The crude product was purified by preparative TLC to give target compound as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 - 7.45 (m, 2H), 7.39 - 7.36 (m, 2H), 7.24 - 7.21 (m, 1H), 7.03 - 7.01 (m, 1H), 6.83 (s, 1H), 4.11 (s, 2H), 3.89 - 3.84 (s, 2H), 3.33 - 3.31 (m, 2H), 2.72 - 2.68 (m, 2H), 1.13 (t, J = 6.9 Hz, 3H), 1.04 (s, 3H), 1.00 (s, 6H). HPLC = 95.3%, (214 nm), 95.7% (254 nm), t_R = 4.26 min. LC-MS: m/z = 478.1 $[M+H]^+$.

[00469] Example #50: Prepared from **Example #51** following the procedure described for **Example #88**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 - 7.37 (m, 4H), 7.25 - 7.23 (m, 1H), 7.05 - 7.03 (m, 1H), 6.85 (s, 1H), 4.11 (s, 2H), 3.89 - 3.87 (s, 2H), 3.32 - 3.29 (m, 5H), 2.62 - 2.58 (m, 2H), 1.14 (t, J = 6.9 Hz, 3H), 1.04 (s, 3H), 1.00 (s, 6H). HPLC = 99.8% (214 nm), 100% (254 nm), t_R = 4.79 min. LC-MS: m/z = 492.1 $[M+H]^+$.

[00470] Scheme 23. Synthesis of Examples #44, 45 46, 48, 53 and 58.



[00471] Step 1: To a mixture of compound **23-32** (2 g, 7.43 mmol) in THF (30 mL) was added NaH (0.54 g, 60%, 22.3 mmol) at r.t, followed by the addition of 1-bromo-2-methoxyethane (1.6 g, 11.2 mmol) and KI (3.7 g, 22.3 mmol). The resulting mixture was stirred at 40 degree overnight. Then the mixture was diluted with H_2O (10 mL), extracted with EA (30 mL X 3). The combined organic layer was washed brine (30 mL), dried over

Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with PE/EA = 4/1, to give product **23-33** as yellow oil. LC-MS: m/z = 328.0 $[M+H]^+$.

[00472] Step 2: Compound **23-34** was prepared using the procedure described in **Scheme 15, Step 1**. LC-MS: m/z = 278.1 $[M+H]^+$.

Step 3: Compound **23-35** was prepared using the procedure described in **Scheme 15, Step 2**. LC-MS: m/z = 280.2 $[M+H]^+$.

[00473] Step 4: Compound **23-36** was prepared using the procedure described in **Scheme 15, Step 3**. LC-MS: m/z = 342.1 $[M+H]^+$.

[00474] Step 5: Compound **23-37** was prepared using the procedure described in **Scheme 15, Step 4**. LC-MS: m/z = 406.1 $[M+H]^+$.

[00475] Step 6: Compound **23-38** was prepared using the procedure described in **Scheme 16, Step 3**. LC-MS: m/z = 438.1 $[M+H]^+$.

[00476] Example #45: ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 - 7.31 (m, 5H), 6.94 - 6.90 (m, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 4.12 (s, 2H), 3.94 (t, *J* = 5.4 Hz, 2H), 3.62 (t, *J* = 5.4 Hz, 2H), 3.35 - 3.29 (m, 5H), 2.70 - 2.66 (m, 2H), 1.06 (s, 6H), 0.67 - 0.62 (m, 2H), 0.48 - 0.43 (m, 2H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.17 min. LC-MS: m/z = 504.1 $[M+H]^+$.

[00477] Example #46: was prepared following the procedure for **Example #45**, but using 1-bromo-2-(2-bromoethoxy)ethane in **step 7** : ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 - 7.34 (m, 5H), 7.06 - 7.03 (m, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 4.16 (s, 2H), 3.99 - 3.95 (m, 4H), 3.64 (t, *J* = 5.4 Hz, 2H), 3.36 - 3.26 (m, 5H), 2.67 - 2.57 (m, 2H), 2.37 - 2.33 (m, 2H), 1.08 (s, 6H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.36 min. LC-MS: m/z = 508.1 $[M+H]^+$.

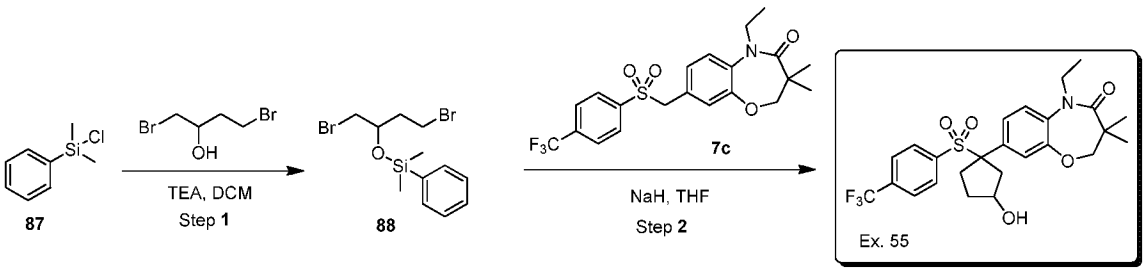
[00478] Example #48: was prepared as described in **Scheme 23** except (bromomethyl)cyclopropane was used in **step 1** instead of 1-bromo-2-methoxyethane: ^1H NMR (300 MHz, CD_3OD) *δ* 7.47 - 7.46 (m, 4H), 7.23 - 7.22 (m, 1H), 7.03 - 7.02 (m, 1H), 6.83 (s, 1H), 4.14 (s, 2H), 3.78 - 3.76 (s, 2H), 3.31 - 3.30 (m, 5H), 2.76 - 2.72 (m, 2H), 1.02 - 0.97 (m, 7H), 0.52 - 0.44 (s, 6H), 0.18 - 0.16 (s, 2H),. HPLC = 98.6% (214 nm), 98.9% (254 nm), t_R = 5.59 min. LC-MS: m/z = 500.1 $[M+H]^+$.

[00479] Example #58: was prepared following the procedure for **Example #48**, but using 1-bromo-2-(2-bromoethoxy)ethane in **step 7**: ^1H NMR (300 MHz, CD_3OD) *δ* 7.47 - 7.03 (m, 7H), 4.17 (s, 2H), 3.80 - 3.77 (s, 2H), 3.77 - 3.75 (m, 2H), 2.31 - 3.29 (m, 2H), 2.55 - 2.50 (m, 4H), 1.29 - 0.98 (s, 7H), 0.45 - 0.43 (s,2H), 0.20 - 0.18 (s,2H). HPLC = 95.4% (214 nm), 95.3% (254 nm), t_R = 4.93 min. LC-MS: m/z = 504.1 $[M+H]^+$.

[00480] Example #44: was prepared as described in **Scheme 23** except 2,2,2-trifluoroethyl trifluoromethanesulfonate was used in **step 1** instead of 1-bromo-2-methoxyethane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.32 (m, 4H), 7.13 - 7.10 (m, 1H), 6.71 - 6.62 (m, 2H), 4.59 (q, *J* = 8.7 Hz, 2H), 3.82 (s, 2H), 3.30 - 3.26 (m, 2H), 2.69 - 2.64 (m, 2H), 1.33 (s, 6H), 0.64 - 0.58 (m, 2H), 0.46 - 0.40 (m, 2H). HPLC = 96.7% (214 nm), 97.8% (254 nm), t_R = 6.64 min. LC-MS: m/z = 528.0 $[M+H]^+$.

[00481] Example #53: was prepared as described for **Example #44** except 1-bromo-2-(2-bromoethoxy)ethane was used in **step 7** instead of cyclopropane-1,1-diylbis(methylene) dimethanesulfonate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.26 (m, 4H), 7.21 - 7.12 (m, 1H), 6.90 - 6.71 (m, 2H), 4.68 - 4.54 (m, 2H), 3.94 (d, *J* = 9.7 Hz, 2H), 3.83 (s, 2H), 3.40 - 3.25 (m, 2H), 2.62 - 2.48 (m, 2H), 2.42 - 2.27 (m, 2H), 1.34 (s, 6H). HPLC = 96.4% (214 nm), 96.5% (254 nm), t_R = 5.88 min. LC-MS: m/z = 532.1 $[M+H]^+$.

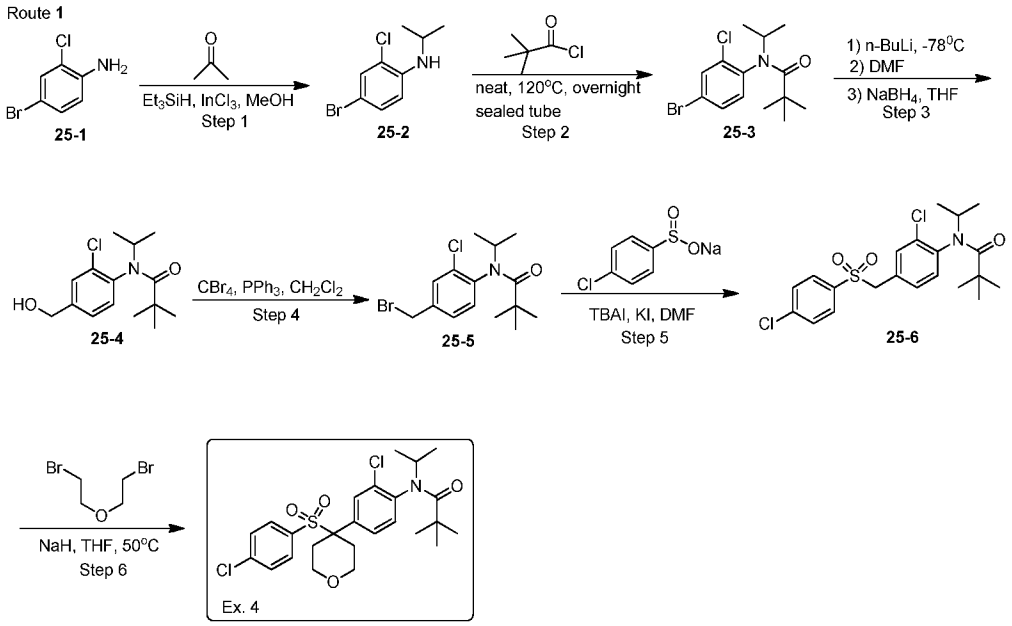
[00482] Scheme 24. Synthesis of Example #55.



[00483] Step 1: To a mixture of compound **24-87** (1 g, 4.3 mmol), TEA (0.87 g, 8.6 mmol) in DCM (30 mL) was added 1,4-dibromobutan-2-ol (0.88 g, 5.16 mmol) and the mixture was stirred at r.t for 3 hrs. The mixture was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography, eluting with PE/EA = 20/1, to give the product **24-88** as a colorless oil.

[00484] Example #55: Prepared from compound **24-88** following the same procedure described for **Example #95**. ^{1}H NMR (300 MHz, CD_3OD) *δ* 7.89 - 7.83 (m, 4H), 7.24 - 6.97 (m, 3H), 4.54 - 4.52 (m, 1H), 4.22 - 4.18 (m, 1H), 4.07 - 4.02 (m, 1H), 3.90 - 3.88 (m, 2H), 2.98 - 2.29 (m, 4H), 1.72 - 1.63 (m, 1H), 1.45 - 1.42 (m, 1H), 1.16 - 1.12 (m, 3H), 0.99 - 0.94 (m, 6H). HPLC = 97.7% (214 nm), 97.3% (254 nm), t_R = 4.89 min. LC-MS: m/z = 512.1 $[M+H]^+$.

[00485] Scheme 25. Synthesis of Example #4, 101, 103, 104, 106, 107, 108, and 109.



[00486] Step 1: 4-bromo-2-chlorobenzenamine **25-1** (0.5 g, 2.4 mmol), Et_3SiH (0.56 g, 4.8 mmol), acetone (0.28 g, 4.8 mmol) and $InCl_3$ (0.16 g, 0.72 mmol) were dissolved in methanol (20 mL). The mixture was stirred at room temperature overnight. The solvent was removed by reduced pressure, and the residue was purified by flash column chromatography (PE/EA = 10/1) to give the product **25-2** as yellow oil. LC-MS: m/z = 247.9 $[M+H]^+$.

[00487] Step 2: Compound **25-2** (5.0 g, 20 mmol) and pivaloyl chloride (3.6 g, 30 mmol) were stirred in sealed tube at 120 °C overnight. Water (80 mL) was added, and the mixture was extracted by DCM (60 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (PE/EA = 10/1) to give the product **25-3** as yellow solid. LC-MS: m/z = 332.0 $[M+H]^+$.

[00488] Step 3: n-BuLi (0.7 mL, 1.65 mmol) was added to a solution of compound **25-3** (0.5 g, 1.5 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 0.5h at -78 °C. Then DMF (0.2 g, 3.0 mmol) was added. The reaction was stirred for another 0.5h at -78 °C. Methanol (3 mL) was added, then $NaBH_4$ (0.11 g, 3.0 mmol) was added at 0 °C. The reaction mixture was further stirred for 0.5h. The mixture was extracted with EA (30 mL x 3). Combined organic layers was washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (PE/EA = 5/1) to give the product **25-4** as white solid. LC-MS: m/z = 284.2 $[M+H]^+$.

[00489] Step 4: The solution of compound **25-4** (0.1 g, 0.35 mmol) and PPh_3 (0.093 g, 0.35 mmol) in DCM (10 mL) was added CBr_4 (0.11 g, 0.35 mmol) at rt. The mixture was stirred at

rt for 0.5h. Water (15 mL) was added. The mixture was extracted with DCM (10 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (PE/EA = 10/1) to give the product **25-5** as yellow oil. LC-MS: m/z = 345.9 $[M+H]^+$.

[00490] **Step 5**: The solution of compound **25-5** (0.06 g, 0.17 mmol), sodium 4-chlorobenzenesulfinate (0.037 g, 0.187 mmol), TBAI (0.031 g, 0.085 mmol) and KI (0.028 g, 0.17 mmol) in DMF (10 mL) was stirred for overnight at rt. Water (10 mL) was added. The mixture was extracted with EA (20 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA = 2/1) to give the product **25-6** as white solid. LC-MS: m/z = 441.9 $[M+H]^+$.

[00491] **Example #4:** The solution of compound **25-6** (100 mg, 0.23 mmol) in THF (10 mL) was NaH (140 mg, 9.7 mmol, 60%w/w) at rt. Then 1-bromo-2-(2-bromoethoxy)ethane (70 mg, 0.3 mmol) was added and stirred overnight at 50 °C. The mixture was cooled to room temperature. Water (10 mL) was added. The mixture was extracted with DCM (15 mL x 3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by pre-TLC and pre-HPLC to give the desired product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.15 (m, 7H), 4.62 (brs, 1H), 4.02 - 3.98 (m, 2H), 3.28 (t, J = 11.4 Hz, 2H), 2.66 - 2.64 (m, 2H), 2.38 - 2.36 (m, 2H), 1.51 (s, 3H), 1.25 - 1.05 (m, 12H). HPLC = 99.2% (214 nm), 99.6% (254 nm), t_R = 5.14 min. LC-MS: m/z = 511.9 $[M+H]^+$.

[00492] **Example # 101**: was prepared following the procedure for **Example #4**, except 4-bromo-3-chloroaniline was used as starting material in **step 1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 1H), 7.35 (s, 4H), 7.13 - 7.04 (m, 2H), 4.95 - 4.87 (m, 1H), 4.08 - 4.01 (m, 2H), 3.55 - 3.29 (m, 3H), 2.74 - 2.54 (m, 3H), 1.07 - 1.02 (m, 15H). HPLC = 99.4% (214 nm), 99.5% (254 nm), t_R = 5.13 min. LC-MS: m/z = 511.9 $[M+H]^+$.

[00493] **Example #103**: was prepared following the procedure for **Example #4**, except sodium 3-chloro-4-methylbenzenesulfinate was used in step 5**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.12 (m, 6H), 4.62 - 4.58 (m, 1H), 4.01 - 3.97 (m, 2H), 3.30 - 3.23 (m, 2H), 2.64 - 2.63 (m, 2H), 2.42 - 2.33 (m, 5H), 1.26 - 1.05 (m, 15H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.38 min. LC-MS: m/z = 525.9 $[M+H]^+$.

[00494] **Example #104**: was prepared following the procedure for **Example #4**, except step 6 was replaced with **steps 1** and **2** of **Scheme 21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.07 (m, 7H), 4.61 - 4.57 (m, 1H), 2.72 - 2.60 (m, 3H), 1.42 - 1.40 (m, 2H), 1.29 - 1.02 (m, 15H) ,

1.02 - 1.00 (m, 1H). HPLC = 99.4% (214 nm), 99.3% (254 nm), t_R = 5.94 min. LC-MS: m/z = 507.9 $[M+H]^+$.

[00495] Example #106: was prepared following the procedure for **Example #4**, except sodium 3-chloro-4-fluorobenzenesulfinate was used in **step 5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 - 7.13 (m, 6H), 4.65 (s, 1H), 4.04 - 4.00 (m, 2H), 3.32 - 3.25 (m, 2H), 2.65 - 2.61 (m, 2H), 2.38 - 2.33 (m, 2H), 1.27 - 1.06 (m, 15H). HPLC = 99.5% (214 nm), 99.9% (254 nm), t_R = 5.22 min. LC-MS: m/z = 529.9 $[M+H]^+$.

[00496] Example #107: was prepared following the procedure for **Example #4**, except oxybis(ethane-2-1diyl)dimethylsulfonate was used in **step 6**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.51 - 7.12 (m, 7H), 3.37 - 3.35 (m, 3H), 2.79 - 2.75 (m, 2H), 1.29 - 1.01 (m, 15H), 0.63 - 0.46 (m, 4H). HPLC = 96.2% (214 nm), 95.4% (254 nm), t_R = 5.92 min. LC-MS: m/z = 508.0 $[M+H]^+$.

[00497] Example #108: was prepared following the procedure for **Example #4**, except sodium 3-fluorobenzenesulfinate was used in **step 5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 - 7.77 (m, 2H), 7.59 - 7.52 (m, 2H), 7.31 - 7.15 (m, 3H), 4.59 - 4.57 (m, 1H), 4.02 - 3.98 (m, 2H), 3.30 - 3.23 (m, 2H), 2.67 - 2.63 (m, 2H), 2.37 - 2.32 (m, 2H), 1.26 - 1.22 (m, 3H), 1.08 - 1.05 (m, 12H). HPLC = 99.6% (214 nm), 99.5% (254 nm), t_R = 5.28 min. LC-MS: m/z = 546.0 $[M+H]^+$.

[00498] Example #109: was prepared following the procedure for **Example #4**, except n-butyl lithium and dihydro-2*H*-pyran-3(4H)-one were used in **step 6**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.53 - 7.29 (m, 7H), 4.65 - 4.52 (m, 2H), 4.17 - 4.13 (m, 1H), 4.85 - 4.79 (m, 1H), 3.57 - 3.49 (m, 1H), 2.76 - 2.69 (m, 1H), 2.62 - 2.52 (m, 1H), 1.77 - 1.67 (m, 1H), 1.51 - 1.39 (m, 1H), 1.29 - 1.01 (m, 15H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.38 min. LC-MS: m/z = 511.9 $[M+H]^+$.

[00499] Example #122: was prepared according to the procedures described in **Scheme 25**, except using sodium-3-fluorobenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 - 7.05 (m, 7H), 4.63 (s, 1H), 4.01 (d, *J* = 11.4 Hz, 2H), 3.29 (t, *J* = 11.6 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.38 (d, *J* = 13.8 Hz, 2H), 1.13 - 1.03 (m, 15H). LC-MS: m/z = 496.1 $[M+H]^+$.

[00500] Example #123: was prepared as described in **Scheme 25**, except using sodium-4-trifluoromethoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.21 - 7.19 (m, 5H), 4.63 (s, 1H), 4.02 (d, *J* = 11.1 Hz, 1H), 3.29 (t, *J* = 11.8 Hz, 2H), 2.69 – 2.66 (m, *J* = 17.8, 7.9 Hz, 2H), 2.38 (d, *J* = 13.3 Hz, 2H), 1.13 - 1.08 (m, 15H). LC-MS: m/z = 562.1 $[M+H]^+$.

[00501] Example #124: was prepared as described in **Scheme 25**, except using sodium-3,4-dichloromethoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 - 7.13 (m, 6H), 4.61 (s, 1H), 4.01 (d, *J* = 9.8 Hz, 2H), 3.29 (t, *J* = 11.5 Hz, 2H), 2.67 - 2.63 (m, 2H), 2.35 (d, *J* = 13.8 Hz, 2H), 1.15 - 1.06 (m, 15H). LC-MS: m/z = 546.0 [M+H]+.

[00502] Example #125: was prepared as described in **Scheme 25**, except sodium-3-fluoro-4-methoxybenzenesulfinate was used in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 - 6.88 (m, 6H), 4.63 (s, 1H), 3.99 - 3.95 (m, 5H), 3.28 (t, *J* = 11.3 Hz, 2H), 2.65 - 2.61 (m, 2H), 2.36 (d, *J* = 14.0 Hz, 2H), 1.13 - 1.05 (m, 15H). LC-MS: m/z = 526.1 $[M+H]^+$.

[00503] Example #126: was prepared as described **in Scheme 25**, except using sodium-3-cyanobenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 - 7.18 (m, 7H), 4.63 (s, 1H), 4.02 (d, *J* = 12.0 Hz, 2H), 3.29 (t, *J* = 11.1 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.36 (d, *J* = 15.5 Hz, 2H), 1.16 - 1.06 (m, 15H). LC-MS: m/z = 503.0 $[M+H]^+$.

[00504] Example #127: was prepared as described in **Scheme 25**, except using sodium-3-methoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 - 6.87 (m, 7H), 4.60 (s, 1H), 4.00 (d, *J* = 11.6 Hz, 2H), 3.80 (s, 3H), 3.27 (t, *J* = 11.7 Hz, 2H), 2.68 - 2.63 (m, 2H), 2.41 (s, 2H), 1.13 (m, 15H). LC-MS: m/z = 508.2 $[M+H]^+$.

[00505] Example #128: was prepared as described in **Scheme 25**, except using sodium-4-methoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 - 7.19 (m, 5H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.63 (s, 1H), 3.99 (d, *J* = 11.2 Hz, 2H), 3.84 (s, 3H), 3.28 (t, *J* = 11.6 Hz, 2H), 2.65 - 2.63 (m, 2H), 2.35 (d, *J* = 11.8 Hz, 2H), 1.13 - 1.08 (m, 15H). LC-MS: m/z = 508.2 $[M+H]^+$.

[00506] Example #129: was prepared as described in **Scheme 25**, except using sodium-3-chloro-4-methoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.13 (m, 5H), 6.86 (d, *J* = 8.6 Hz, 1H), 4.61 (s, 1H), 3.98 (d, *J* = 18.4 Hz, 5H), 3.27 (t, *J* = 11.1 Hz, 2H), 2.64 (t, *J* = 10.6 Hz, 2H), 2.35 (d, *J* = 13.8 Hz, 2H), 1.17 - 1.06 (m, 15H). LC-MS: m/z = 542.1 $[M+H]^+$.

[00507] Example #130: was prepared as described in **Scheme 25**, except using sodium-4-cyanobenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.21 - 7.19 (m, 3H), 4.65 (s, 1H), 4.02 (d, *J* = 11.1 Hz, 2H), 3.30 (t, *J* = 11.6 Hz, 2H), 2.67 (t, *J* = 10.4 Hz, 2H), 2.36 (d, *J* = 13.0 Hz, 2H), 1.15 - 1.10 (m, 15H). LC-MS: m/z = 503.1 $[M+H]^+$.

[00508] Example #131: was prepared as described in **Scheme 25**, except using sodium-3-trifluoromethoxybenzenesulfinate in **step 5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 7H), 4.60 (s, 1H), 4.01 - 3.94 (m, 2H), 3.28 - 3.21 (m, 2H), 2.66 - 2.61 (m, 2H), 2.36 (d, *J* = 13.7 Hz, 2H), 1.13 - 1.05 (m, 15H). LC-MS: m/z = 562.1 $[M+H]^+$.

[00509] Example #132: was prepared as described in **Scheme 25.** ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.87Hz, 2H), 7.55 (d, *J* = 8.87 Hz, 2H) 7.33 (d, *J* = 1.7 Hz, 1H) 7.27 (d, *J* = 8.03 HZ, 1H) 7.18 (dd, *J* = 8.03, 1.7 Hz, 1H) 4.62 (s, 2H), 4.54 (br.s, 1H) 1.02 (d, *J* = 6.63 Hz, 3H), 0.97 (d, *J* = 6.78 Hz, 3H).LC-MS: m/z = 441.9 [M+H]+.

[00510] Example #133: was prepared as described in **Scheme 25**, except using 4-bromo-2-chloroaniline in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 4H), 7.14 – 6.98 (m, 3H), 4.945 – 4.85 (m, 1H), 4.03 – 3.99 (m, 2H), 3.29 (t, *J* = 11.7 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.37 – 2.62 (m, 2H), 1.07 – 1.04 (m, 15H). LC-MS: m/z = 495.9 $[M+H]^+$.

[00511] Example #134: was prepared as described in **Scheme 25**, except using 4-bromo-2-chloroaniline in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 - 7.40 (m, 4H), 7.08 - 6.87 (m, 3H), 4.90 - 4.85 (m, 1H), 4.33 (s, 2H), 1.01 - 0.88 (m, 15H). LC-MS: m/z = 425.9 $[M+H]^+$.

[00512] Example #135: was prepared as described in **Scheme 25**, except using 4-bromo-2-chloroaniline in step 1 and cyclobutanecarbonyl chloride in **step 2**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 4H), 7.11 – 7.04 (m, 3H), 5.01 – 4.92 (m, 1H), 4.04 – 4.01 (m, 2H), 3.36 – 3.29 (m, 2H), 2.70 – 2.63 (m, 3H), 2.39 – 2.25 (m, 4H), 1.81 – 1.66 (m, 4H),1.11 – 0.99 (m, 6H). LC-MS: m/z = 493.9 $[M+H]^+$.

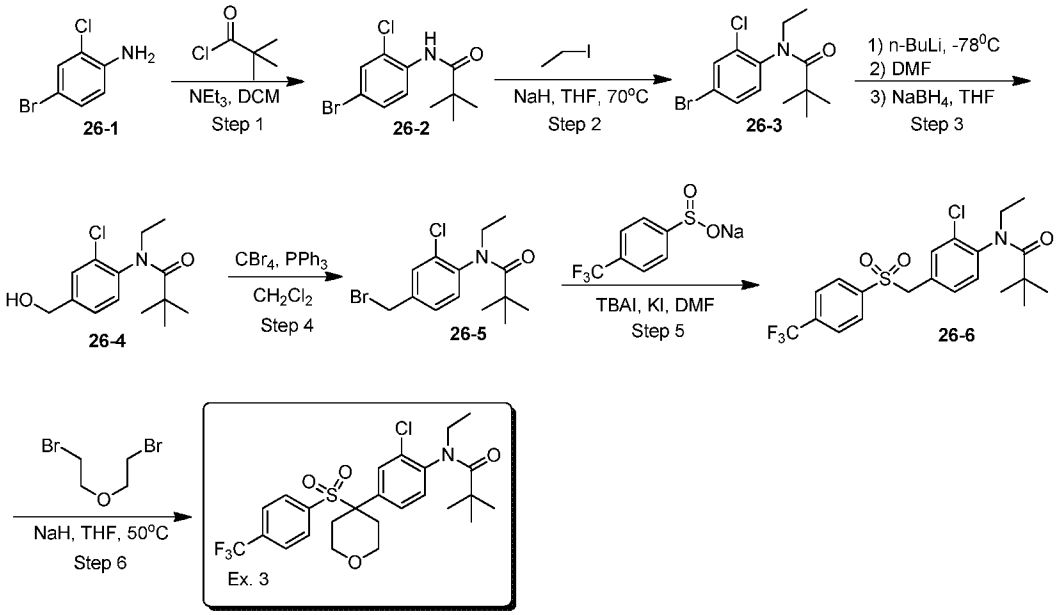
[00513] Example #136: was prepared as described in **Scheme 25**, except using 4-bromo-2-chloroaniline in step 1 and cyclobutanecarbonyl chloride in **step 2**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.43 (m, 4H), 7.03 – 6.91 (m, 3H), 4.98 – 4.89 (m, 1H), 4.33 (s, 2H), 2.76 – 2.68 (m, 2H), 2.34 – 2.23 (m, 2H), 1.74 – 1.52 (m, 4H),1.08 – 0.96 (m, 6H). LC-MS: m/z = 424.1 $[M+H]^+$.

[00514] Example #137: was prepared as described in **Scheme 25**, except using 4-bromo-2-methylaniline in step 1 and cyclobutanecarbonyl chloride in **step 2**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.14 – 6.91 (m, 3H), 4.86 – 4.77 (m, 1H), 4.05 – 3.97 (m, 2H), 3.40 – 3.28 (m, 2H), 2.71 – 2.39 (m, 6H), 2.22 – 2.07 (m, 4H), 1.83 – 1.59 (m, 4H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). LC-MS: m/z = 490.0 $[M+H]^+$.

[00515] Example #138: was prepared as described in **Scheme 25**, except using 4-bromo-2-chloroaniline in step 1 and 1,1-bis(iodomethyl)cyclopropane in **step 6**. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.35 – 7.25 (m, 4H), 6.94 – 6.80 (m, 3H), 4.57 – 4.48 (m, 1H), 3.35 – 3.29 (m, 2H), 2.77 – 2.69 (m, 2H), 2.16 (s, 3H), 1.25 – 0.94 (m,15H), 0.72 – 0.66 (m, 2H), 0.51– 0.45 (m, 2H). LC-MS: m/z = 488.0 $[M+H]^+$.

[00516] Scheme 26. Synthesis of Examples #3, 18, 24, 38, 39, 40, 41, and 42.



[00517] Step 1: Pivaloyl chloride (0.7 g, 5.76 mmol) was added to a solution of compound **26-1** (1.0 g, 4.8 mmol) and Et_3N (1.0 g, 9.6 mmol) in DCM (40 mL). The mixture was stirred at room temperature overnight. Water (50 mL) was added. The mixture was extracted with DCM (40 mL x 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the product **26-2** as colorless oil. LC-MS: m/z = 289.9 $[M+H]^+$.

[00518] Step 2: The solution of compound **26-2** (7.6 g, 26 mmol) in THF (100 mL) was added NaH (3.1 g, 78 mmol). The mixture was stirred at rt for 0.5h. Then EtI (8.2 g, 52 mmol) was added, and stirred at 70 °C overnight. The mixture was cooled to rt. Water (120 mL) was added. The mixture was extracted with EA (80 mL x 3). Combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (PE/EA = 10/1) to give the product **26-3** as yellow oil. LC-MS: m/z = 317.9 $[M+H]^+$.

[00519] Step 3: The same procedure with the step 3 of **Scheme 1** was applied to the preparation of compound **26-4**. LC-MS: m/z = 270.1 $[M+H]^+$.

[00520] Step 4: The same procedure with the **step 4** of **Scheme 1** was applied to the preparation of compound **26-5**. LC-MS: m/z = 332.0 $[M+H]^+$.

[00521] **Step 5**: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of compound **26-6**. LC-MS: m/z = 462.0 $[M+H]^+$.

[00522] **Example #3:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 - 7.53 (m, 4H), 7.23 - 6.98 (m, 3H), 4.18 (brs, 1H), 4.02 - 3.98 (m, 2H), 3.31 (t, *J* = 11.8 Hz, 2H), 3.19 - 3.02 (m, 1H), 2.65 - 2.61 (m, 2H), 2.40 - 2.36 (m, 2H), 1.55 (s, 3H), 1.25 - 1.04 (m, 9H). HPLC = 99.3.% (214 nm), 99.7% (254 nm), t_R = 5.12 min. LC-MS: m/z = 531.9 $[M+H]^+$.

[00523] **Example #18:** was prepared following the procedure for **Example #3**, except sodium 4-chlorobenzenesulfinate was used in **step 5:** ^{1}H NMR (METHANOL-d_4) δ: 7.38 - 7.49 (m, 2H), 7.25 - 7.34 (m, 2H), 6.87 - 6.96 (m, 2H), 6.60 (d, J = 8.3 Hz, 0H), 4.03 (q, J = 7.2 Hz, 2H), 3.85 - 3.98 (m, 2H), 2.35 - 2.55 (m, 3H), 2.01 (s, 3H), 1.28 (t, J = 7.0 Hz, 4H), 1.13 (s, 9H). LC-MS: m/z = 478.0 $[M+H]^+$.

[00524] **Example #38:** was prepared following the procedure for **Example #18**, except 4-bromo-2-(trifluoromethyl)aniline was used as starting material in **step 1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 - 7.51 (m, 1H), 7.39 - 7.26 (m, 6H), 4.37 - 4.16 (m, 2H), 4.08 - 3.94 (m, 2H), 3.36 - 3.12 (m, 2H), 2.75 - 2.54 (m, 2H), 2.49 - 2.33 (m, 2H), 1.28 - 0.99 (m, 12H). HPLC = 98.0% (214 nm), 97.5% (254 nm), t_R = 5.10 min. LC-MS: m/z = 532.2 $[M+H]^+$.

[00525] **Example #39:** was prepared following the procedure for **Example #38**, except 4-bromo-2-(trifluoromethyl)aniline was used as starting material in **step 1** and oxybis(ethane-2,1-diyl)dimethylsulfonate was used in **step 6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 - 7.54 (m, 4H), 7.43 - 7.40 (m, 1H), 7.20 - 7.07 (m, 2H), 4.29 - 4.22 (m, 1H), 3.41 - 3.35 (m, 2H), 3.15 - 2.73 (m, 3H), 1.15 - 1.11 (m, 12H), 0.70 - 0.65 (m, 2H), 0.53 - 0.47 (m, 2H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 5.96 min. LC-MS: m/z = 562.2 $[M+H]^+$.

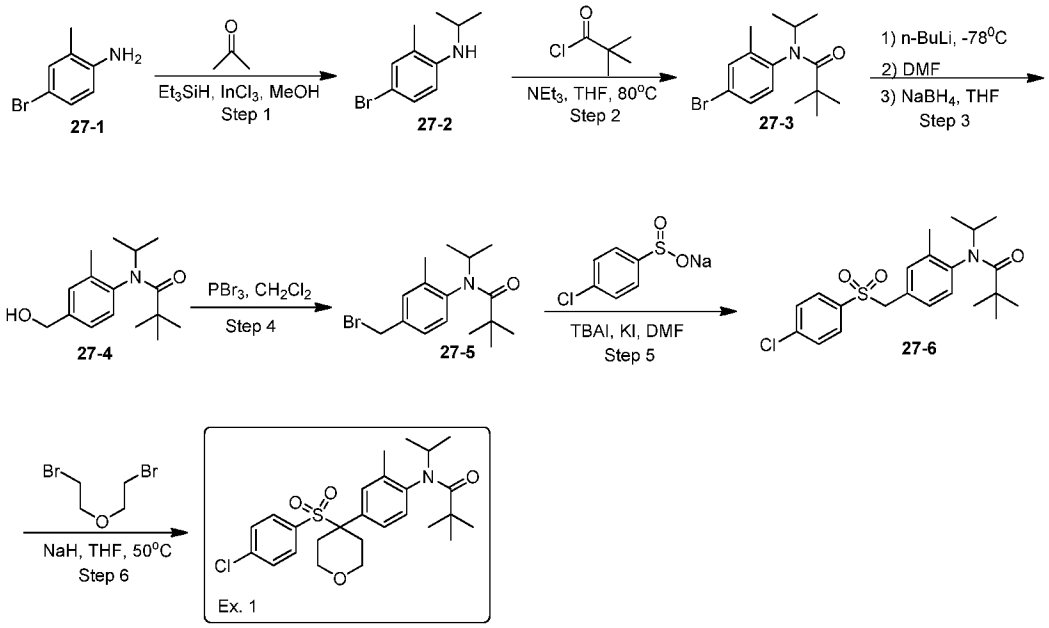
[00526] **Example #42:** was prepared following the procedure for **Example #3**, except 4-bromoaniline was used as starting material in **step 1** and sodium 3 (trifluoromethyl) benzenesulfinate was used in **step 5**: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.83 - 7.82 (m, 1H), 7.59 - 7.52 (m, 3H), 7.25 - 7.15 (m, 4H), 4.02 - 3.98 (m, 2H), 3.72 - 3.70 (m, 2H), 3.29 - 3.25 (m, 2H), 2.67 - 2.64 (m, 2H), 2.42 - 2.37 (m, 2H), 1.12 - 1.10 (m, 3H), 1.04 (s, 9H). HPLC = 100% (214 nm), 100% (254 nm), t_R = 4.84 min. LC-MS: m/z = 498.2 $[M+H]^+$.

[00527] **Example #40:** was prepared following the procedure for **Example #42**, except sodium 4- (trifluoromethyl) benzenesulfinate was used in **step 5**: LC-MS: m/z = 494 $[M+H]^+$.

[00528] **Example #41:** was prepared following the procedure for **Example #42**, except oxybis(ethane-2-1-diyl)dimethanesulfonate was used in **step 6**: LC-MS: m/z = 498 $[M+H]^+$.

[00529] Example #24: was prepared following the procedure for **Example #18**, except 4-bromo-2-methylaniline was used as starting material in**step 1**: LC-MS: m/z = 479 $[M+H]^+$.

[00530] Scheme 27. Synthesis of Example #1



[00531] Step 1: The same procedure with the **step 1** of **Scheme 1** was applied to the preparation of compound **27-2**. LC-MS: m/z = 228.0 $[M+H]^+$.

[00532] Step 2: The same procedure with the step 2 of **Scheme 1** was applied to the preparation of compound **27-3**. LC-MS: m/z = 312.1 $[M+H]^+$.

[00533] Step 3: The same procedure with the **step 3** of **Scheme 1** was applied to the preparation of compound **27-4**. LC-MS: m/z = 264.1 $[M+H]^+$.

[00534] Step 4: To a solution of Compound **3a-4** (0.31 g, 1.18 mmol) in DCM (10 mL) was added PBr_3 (0.32 g, 1.18 mmol) at 0 degree. The mixture was stirred at 0 degree for 2 hrs and then poured into ice water (10 mL). The mixture was extracted with DCM (10 mL X 3). The combined organic layer was washed brine (10 mL), dried over Na_2SO_4 and concentrated give crude compound **27-5** as yellow oil. LC-MS: m/z = 326.0 $[M+H]^+$.

[00535] Step 5: The same procedure with the **step 5** of **Scheme 1** was applied to the preparation of compound **27-6**. LC-MS: m/z = 422.1 $[M+H]^+$.

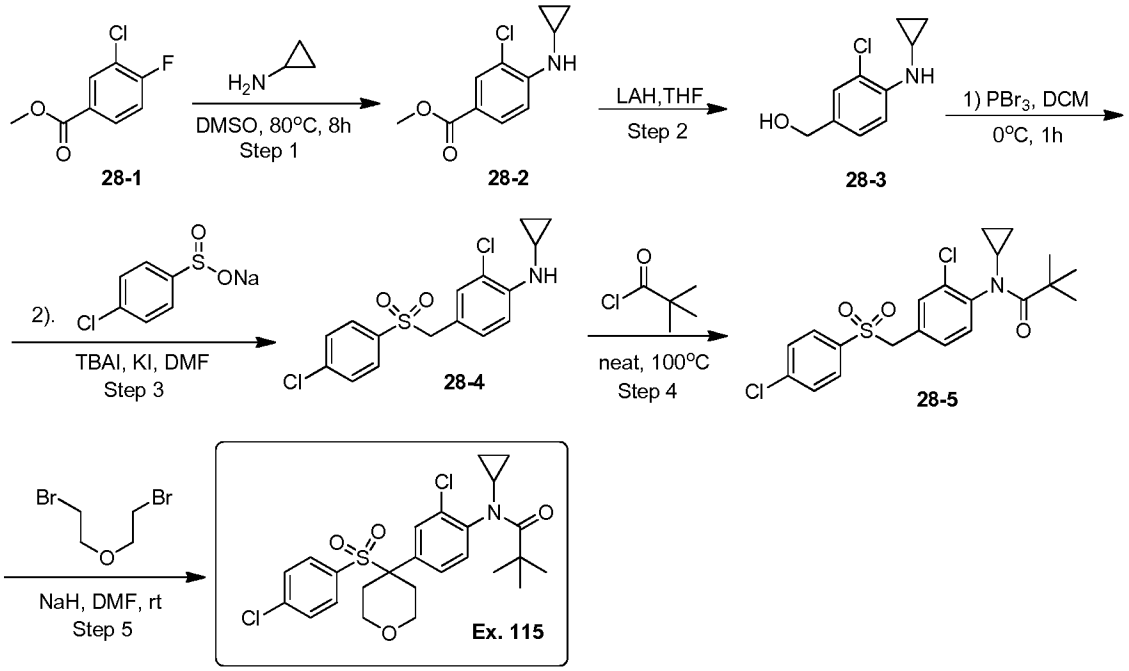
[00536] Step 6: The same procedure with the **step 6** of **Scheme 1** was applied to the preparation of **Example #1**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 - 7.25 (m, 4H), 7.02 - 6.99 (m, 3H), 4.58 (brs, 1H), 3.31 (d, *J* = 9.3 Hz, 2H), 3.29 (t, *J* = 11.5 Hz, 2H), 2.65 - 2.60 (m, 2H), 2.40 - 2.36 (m, 2H), 2.19 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.04 - 0.95 (m, 12H). HPLC

= 99.7.% (214 nm), 98.4% (254 nm), t_R = 5.01 min. LC-MS: m/z = 492.0 $[M+H]^+$.

[00537] Example #112: was prepared following the procedure described in **Example #23**, except using 1,1-bis(iodomethyl)cyclopropane in **step 2**. ^{1}H NMR (301 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.4 Hz, 1H), 7.89 – 7.54 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 1H), 3.79 (q, *J* = 7.2 Hz, 2H), 3.38 (d, *J* = 13.8 Hz, 2H), 2.76 (d, *J* = 13.8 Hz, 2H), 1.23 – 1.03 (m, 12H), 0.71 – 0.59 (m, 2H), 0.56 – 0.42 (m, 2H). . LC-MS: m/z = 495.0 $[M+H]^+$.

[00538] PREPARATIVE EXAMPLE #115

[00539] Scheme 28.



[00540] Step 1: A mixture of compound **28-1** (1.5 g, 7.9.5 mmol), cyclopropanamine (1.36 g, 23.9 mmol) in DMSO (5 mL) was stirred at 80°C for 8 h. The reaction was quenched with water and extracted with EA (10 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1) to give **28-2** as a yellow oil. LC-MS: m/z = 226.0 $[M+H]^+$.

[00541] Step 2: To a 0°C solution of compound **28-2** (0.6 g, 2.66 mmol) in THF (40 mL) was added $LiAlH_4$ (0.202 g, 5.32 mmol). The reaction was stirred for 2 hrs. then quenched with water and 10% NaOH aqueous solution. The resulting mixture was filtered and the filtrate evaporated to give crude **28-3** as a colorless oil. LC-MS: m/z = 198.1 $[M+H]^+$.

[00542] Step 3: To a 0°C solution of compound **28-3** (0.456 g, 2.3 mmol) in CH_2Cl_2 (10

mL) was added PBr_3 (0.623g, 2.3 mmol). The reaction was stirred for 1 hr. and poured into a mixture of sodium 4-chlorobenzenesulfinate (0.548 g, 2.76 mmol), TBAI (0.17 g, 0.46 mmol) and KI (0.458 g, 2.76 mmol) in DMF (10 mL). The resulting mixture was stirred at room temperature for 3 hrs. The reaction was quenched with water and extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 2/1) to give **28-4** as a white solid. LC-MS: m/z = 323.9 $[M+H]^+$.

[00543] Step 4: The reaction mixture of compound **28-4** (200 mg, 0.56 mmol) and pivaloyl chloride (5 mL) was stirred at 100°C overnight. Then the solvent was evaporated and the residue was purified by prep-TLC (eluent: PE/EA = 2/1) to give **28-5** as a colorless oil. LC-MS: m/z = 439.9 $[M+H]^+$.

[00544] Step 5: To a solution of compound **28-5** (53 mg, 0.12 mmol) in dry DMF (5 mL) was added NaH (15 mg, 0.6 mmol) and 2,2'-dibromodiethyl ether (84 mg, 0.36 mmol) at r.t and then stirred overnight. Water was added and the resulting mixture was extracted with EA (20 mL x 3). The combined organic layers were dried over Na2SO4 and evaporated. The residue was purified by prep-TLC (eluent: PE/EA = 2/1) to give **Example #115** as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.37 – 7.28 (m, 4H), 7.25 – 7.24 (m, 1H), 7.13 – 7.03 (m, 2H), 4.03 – 3.96 (m, 2H), 3.33 – 3.19 (m, 3H), 2.70 – 2.60 (m, 2H), 2.38 – 2.30(m, 2H), 1.16 (s, 9H), 0.87 – 0.79 (m, 2H), 0.50 – 0.43 (m, 2H). LC-MS: m/z = 509.9 [M+H]+.

[00545] Example #116: was prepared as described in **Scheme 28**, except using cyclobutylamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 - 7.07 (m, 7H), 4.97 - 4.95 (m, 1H), 4.04 (d, *J* = 10.9 Hz, 2H), 3.34 (t, *J* = 11.8 Hz, 2H), 2.72 - 2.15 (m, 9H), 1.76 - 1.58 (m, 8H). LC-MS: m/z = 522.0 $[M+H]^+$.

[00546] Example #117: was prepared as described in **Scheme 28**, except using cyclobutylamine in **step 1** and cyclobutanecarbonyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.07 (m, 7H), 4.97 (s, 1H), 4.04 (d, *J* = 10.9 Hz, 2H), 3.34 (t, *J* = 11.8 Hz, 2H), 2.67 – 1.58 (m, 17H). LC-MS: m/z = 522.0 [M+1].

[00547] Example #118: was prepared as described in **Scheme 28**, except using cyclopentylamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.22 - 7.11 (m, 7H), 4.52 (s, 1H), 4.02 - 3.97 (m, 2H), 3.29 (t, *J* = 12.2 Hz, 2H), 2.70 - 2.65 (m, 2H), 2.38 - 2.35 (m, 2H), 2.05 - 2.87 (m, 2H), 1.52 - 1.38(s, 6H), 1.09 (s, 9H). LC-MS: m/z = 537.9 $[M+H]^+$.

[00548] Example #119: was prepared as described in **Scheme 28**, except using 4-bromo-2-methylaniline and cyclopropylmethanamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 –

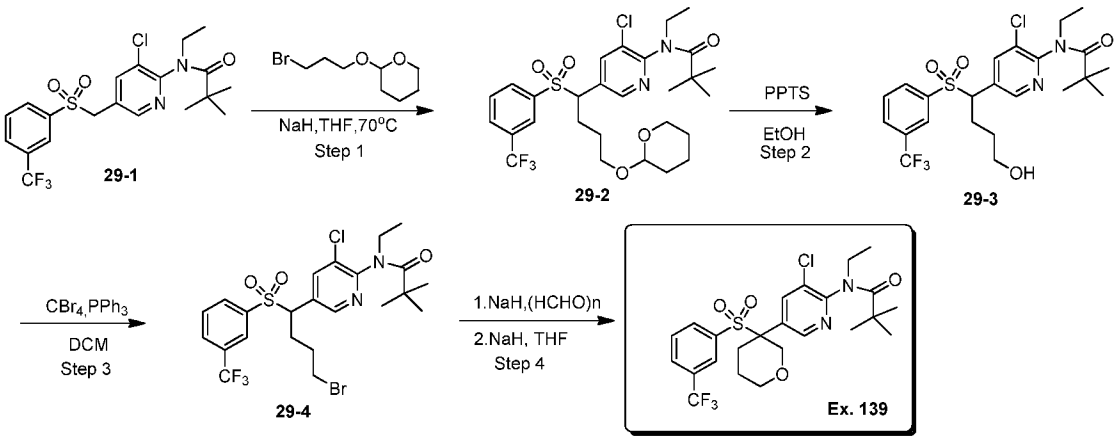
7.31 (m, 4H), 7.20 – 7.12 (m, 2H), 6.99 – 6.96 (m, 2H), 4.14 – 4.08 (m, 1H), 4.01 – 3.97 (m, 2H), 3.34 – 3.25 (m, 2H), 2.66 – 2.62 (m, 2H), 2.42 – 2.38 (m, 2H), 2.20 (s, 3H), 1.26 – 1.00 (m, 10H), 0.44 – 0.41 (m, 2H), 0.16 – 0.10 (m, 1H), -0.03 – -0.09 (m, 1H). LC-MS: m/z = 504.1 $[M+H]^+$.

[00549] Example #120: was prepared as described in **Scheme 28**, except using 4-bromo-2-methylaniline and cyclopentylamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 7.10 – 6.95 (m, 3H), 4.53 – 4.39 (m, 1H), 4.04 – 4.94 (m, 2H), 3.36 – 3.25 (m, 2H), 2.70 – 2.60 (m, 2H), 2.41 – 2.37 (m, 2H), 2.18 (s, 3H), 2.11 – 2.01 (m, 1H), 1.80 – 1.44 (m, 7H), 1.04 (s, 9H).). LC-MS: m/z = 518.0 $[M+H]^+$.

[00550] Example #121: was prepared as described in **Scheme 28**, except using 4-bromo-2-methylaniline and cyclopropylamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 7.13 – 7.00 (m, 3H), 4.85 – 4.74 (m, 1H), 4.02 – 3.95 (m, 2H), 3.31 (t, J = 11.7 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.42 – 2.34 (m, 2H), 2.11 (s, 3H), 2.01 – 1.92 (m, 1H), 1.83– 1.41 (m, 5H), 1.06 (s, 9H). LC-MS: m/z = 504.0 $[M+H]^+$.

[00551] PREPARATIVE EXAMPLE #139

[00552] Scheme 29.



[00553] Step 1: To a mixture of compound **29-1** (prepared as outlined in **Scheme 6**, using sodium 3-(trifluoromethyl)benzenesulfinate in **Step 4**) (0.2 g, 0.43 mmol) in THF (10 mL) was added NaH (21 mg, 0.87 mmol), then followed by 2-(3-bromopropoxy)-tetrahydro-2H-pyran (0.14g, 0.65 mmol) at r.t. The resulting mixture was stirred overnight at 70 °C, quenched with H_2O (10 mL) and extracted with EA (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to the crude product. The crude product was purified by column chromatography eluting with PE/EA = 3/1 to give target compound **29-2** as a colorless oil, 0.08 g. LC-MS: m/z = 626.9 $[M+Na]^+$.

[00554] **Step 2**: A mixture of compound **29-2** (0.91 g, 1.37 mmol), PPTS (35 mg, 0.14 mmol) in EtOH (20 mL) was stirred at 80 °C for 1 hr. and concentrated in vacuo. The residue was diluted with EA (30 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to give target compound **29-3** as a colorless oil. LC-MS: m/z = 521.1 $[M+H]^+$.

[00555] **Step 3**: To a 0 °C mixture of compound **29-3** (0.75 g, 1.44 mmol) and CBr_4 (0.5 g, 1.51 mmol) in DCM (15 mL) was added PPh_3 (0.4 g, 1.51 mmol). The reaction miture was stirred at r.t. for 20 min. the concentrated. The residue was purified by column chromatography eluting with PE/EA = 4/1 to give target compound **29-4** as a colorless oil. LC-MS: m/z = 584.8 $[M+H]^+$.

[00556] **Step 4**: To a 0 °C mixture of compound **1-4** (0.2 g, 0.34 mmol) and NaH (41 mg, 1.72 mmol) in THF (15 mL) was added $(HCHO)_n$ (0.27 g, 3.43 mmol). The reaction was stirred for 2 hrs. then warmed to rt and stirred for another 2 hrs. The reaction was quenched with H_2O (10 mL) and extracted with EA (10 mL x 3). The combined organic layer was washed with brine (10mL), dried over Na_2SO_4 and concentrated. The residue was purified by prep. TLC to give **Example #139** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.90 – 7.73 (m, 3H), 7.63 – 7.53 (m, 2H), 4.47 (d, *J* = 12.3 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 3.90 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.70 (bs, 2H), 3.53 (t, *J* = 10.5 Hz, 1H), 2.64 (d, *J* = 5.4 Hz, 2H), 1.73 (d, *J* = 14.1 Hz, 2H), 1.15 – 1.06 (m, 12H). LC-MS: m/z = 532.9 $[M+H]^+$.

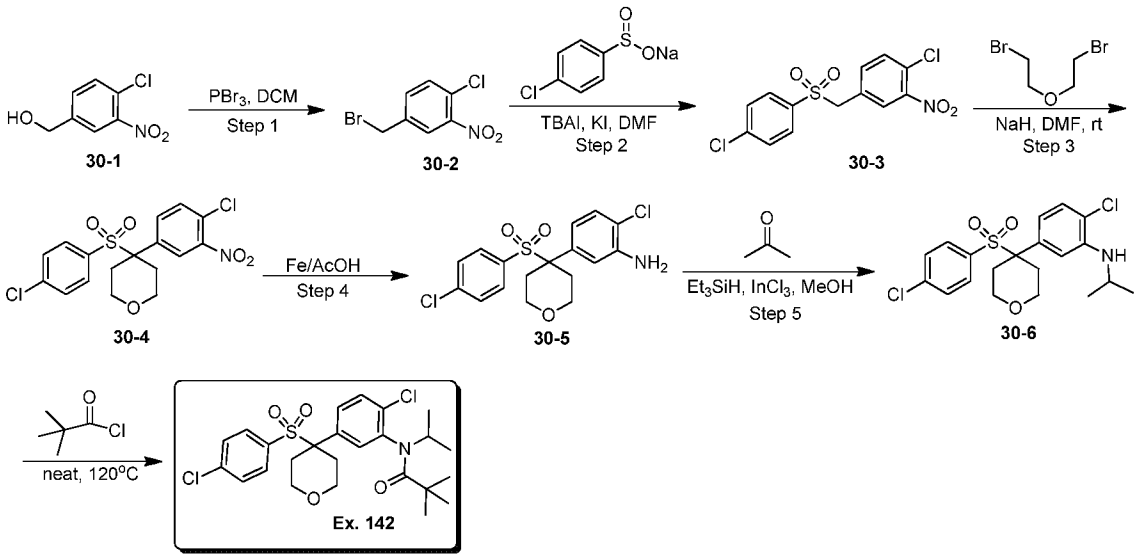
[00557] **Examples #140 and #141** were prepared as described in **Scheme 29**, starting with **Compound 6-6**.

[00558] After cyclisation of the THP ring the two enantiomers were separated by chiral HPLC (Diacel chiralpak OJ-H 250 x 20 mm, 5 um column. Mobile phase MeOH:CO_2 (15:85). Flow rate 40 mL/min.). Enantiomer 1 (first off the column) was labeled **Example #141**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.35 (q, *J* = 8.5 Hz, 4H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 4.00 – 3.42 (m, 4H), 2.63 – 2.55 (m, 2H), 1.73 – 1.50 (m, 2H), 1.19 – 1.02 (m, 12H). LC-MS: m/z = 499.1 $[M+H]^+$.

[00559] Enantiomer 2 (second off the column) was labeled **Example #141**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 2.1 Hz, 1H), 7.35 (q, *J* = 8.7 Hz, 4H), 4.50 (d, *J* = 12.5 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 3.98 – 3.38 (m, 4H), 2.68 – 2.58 (m, 2H), 1.76 – 1.56 (m, 2H), 1.27 – 0.89 (m, 12H). LC-MS: m/z = 499.0 $[M+H]^+$.

[00560] **PREPARATIVE EXAMPLE #142.**

[00561] Scheme 30.



[00562] Step 1: To a 0°C solution of compound **30-1** (0.5 g, 2.67 mmol) in DCM (30 mL) was added PBr_3 (0.87 g, 3.20 mmol) dropwise. The reaction was stirred at 0°C for 1 hr. then quenched with water (10 m L) and extracted with DCM (30 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 10/1) to give **30-2** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.60 – 7.51 (m, 2H), 4.47 (s, 2H).

[00563] Step 2: A mixture of compound **30-2** (0.3 g, 1.2 mmol), sodium 4-chlorobenzenesulfinate (0.29 g, 1.44 mmol), KI (28 mg, 0.24 mmol), TBAI (88 mg, 0.24 mmol) in DMF (50 Ml) was stirred at room temperature for 1h. The crude **30-3** was used directly in next step without purification.

[00564] Step 3: To the crude **30-3** was added NaH (0.14 g, 5.99 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (0.83 g, 3.59 mmol). The mixture was stirred at room temperature for 1 hr. The reaction was quenched with water (10 m L), and extracted with EA (50 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 2/1) to give **30-4** as a colorless oil. LC-MS: m/z = 437.9 $[M+Na]^+$.

[00565] Step 4: A mixture of compound **30-4** (0.29 g, 0.7 mmol) and iron powder (0.2 g, 3.49 mmol) in AcOH (30 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue was diluted with water (30 m L) and basified with $NaHCO_3$ to pH = 7. The mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give **30-5** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.13 – 7.10 (m, 1H), 7.74 – 7.73 (m, 1H), 6.37 – 6.34 (m, 1H), 3.96 – 3.92 (m, 2H), 3.36 – 3.28 (m, 2H), 2.60 – 2.50 (m, 2H), 2.31 – 2.26 (m, 2H). LC-MS: m/z = 407.7 $[M+Na]^+$.

[00566] **Step 5:** A mixture of **30-5** (100 mg, 0.26 mmol), Et_3SiH (60 mg, 0.52 mmol), $InCl_3$ (17 mg, 0.08 mmol) and propan-2-one (30 mg, 0.52 mmol) in MeOH (10 mL) was stirred at room temperature overnight. The mixture was evaporated and the residue was purified by column chromatography (eluent: PE/EA = 1/1) to give **30-6** as a colorless oil. LC-MS: m/z = 427.9 $[M+H]^+$.

[00567] **Step 6:** A mixture of compound **30-6** (70 mg, 0.16 mmol) and pivaloyl chloride (10 mL) was stirred at 120°C overnight. The solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 1/1) to give **Example #142** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 5H), 7.20 – 7.09 (m, 2H), 4.63 – 4.59 (m, 1H), 4.03 – 3.94 (m, 2H), 4.34 – 3.23 (m, 2H), 2.65 – 2.54 (m, 2H), 2.40 – 2.32 (m, 2H), 1.15 – 0.82 (m, 15H). LC-MS: m/z = 512.0 $[M+H]^+$.

[00568] **Example #143:** was prepared as described in **Scheme 30**, except using cyclobutanone in **step 5**.

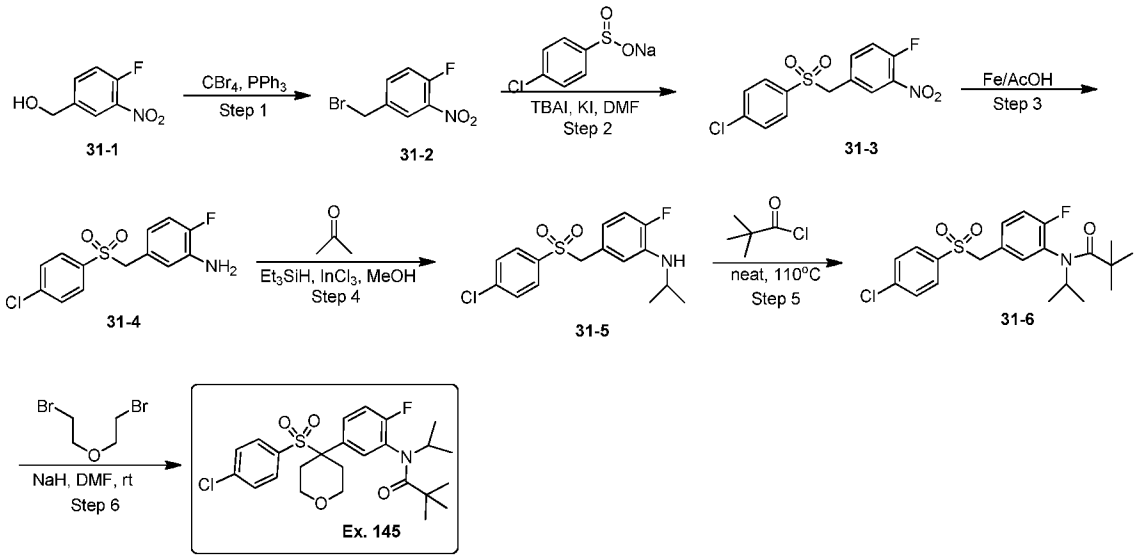
[00569] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 6H), 7.10 – 7.05 (m, 1H), 4.84 – 4.74 (m, 1H), 4.01 – 3.96 (m, 2H), 3.35 – 3.29 (m, 2H), 2.67 – 2.55 (m, 2H), 2.44 – 2.32 (m, 2H), 2.28 – 2.02 (m, 2H), 1.77 – 1.51 (m, 4H), 1.08 (s, 9H). LC-MS: m/z = 524.1 $[M+H]^+$.

[00570] **Example #144:** was prepared as described in **Scheme 30**, except the ethyl substituent was inserted in **Step 5** using sodium hydride and ethyl iodide as outlined in **Scheme 10 Step 1**:

[00571] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 5H), 7.22 – 7.20 (m, 2H), 4.19 – 4.09 (m, 2H), 4.01 (t, *J* = 11.2 Hz, 2H), 3.31 (q, *J* = 12.1 Hz, 2H), 3.08 – 2.99 (m, 1H), 2.64 – 2.57 (m, 2H), 2.45 – 2.34 (m, 2H), 1.09 – 1.04 (m, 12H). LC-MS: m/z = 498.1 $[M+H]^+$.

[00572] **PREPARATIVE EXAMPLE #145.**

[00573] Scheme 31.



[00574] Step 1: To a solution of compound **31-1** (2 g, 11.7 mmol) in DCM (30 mL) was added PBr_3 (3.8 g, 14 mmol) dropwise at 0°C. The reaction mixture was stirred at 0°C for 1 hr. The mixture was quenched with water (50 m L) and extracted with DCM (50 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 10/1) to give **31-2** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.11 – 8.07 (m, 1H), 7.69 – 7.64 (m, 1H), 7.31 – 7.25 (m, 1H), 4.48 (s, 2H).

[00575] Step 2: A mixture of **31-2** (0.5 g, 1.5 mmol), sodium 4-chlorobenzenesulfinate (0.36 g, 1.80 mmol), KI (49 mg, 0.3 mmol), and TBAI (110 mg, 0.3 mmol) in DMF (20 mL) was stirred at room temperature for 1h. The mixture was evaporated and the residue purified by column chromatography (eluent: PE/EA = 2/1) to give **31-3** as a yellow oil. LC-MS: m/z = 351.9 $[M+Na]^+$.

[00576] Step 3: A mixture of **31-3** (0.64 g, 1.49 mmol) and iron powder (0.84 g, 14.9 mmol) in AcOH (30 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue diluted with water (30 m L), basified with $NaHCO_3$ to pH = 7. The mixture was extracted with EA (20 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated to give **31-4** as a yellow oil. LC-MS: m/z = 300.0 $[M+H]^+$.

[00577] Step 4: A mixture of compound **31-4** (300 mg, 1 mmol), Et_3SiH (230 mg, 2 mmol), $InCl_3$ (67 mg, 0.3 mmol) and propan-2-one (120 mg, 2 mmol) in MeOH (100 mL) was stirred at room temperature overnight. The mixture was evaporated and the residue was purified by column chromatography (eluent: PE/EA = 2/1) to give **31-5** as a yellow oil. LC-MS: m/z = 341.9 $[M+H]^+$.

[00578] Step 5: A mixture of compound **31-5** (200 mg, 0.59 mmol) and pivaloyl chloride (20 mL) was stirred at 110°C overnight. The solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 1/1) to give **31-6** as a yellow oil. LC-MS: m/z = 425.9 $[M+H]^+$.

[00579] Step 6: To the mixture of **31-6** (120 mg, 0.28 mmol) in DMF (10 mL) was added NaH (34 mg, 1.41 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (200 mg, 0.85 mmol). The mixture was stirred at room temperature for 1 hr, then quenched with water (10 m L), and extracted with EA (20 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 1/1) to give **Example #145** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.19 – 7.07 (m, 3H), 4.95 – 4.85 (m, 1H), 4.04 – 3.93 (m, 2H), 3.30 (t, *J* = 11.6 Hz, 2H), 2.64 – 2.57 (m, 2H), 2.43 – 2.31 (m, 2H), 1.11 – 0.97 (m, 15H). LC-MS: m/z = 496.1 $[M+H]^+$.

[00580] Example #146: was prepared as described in **Scheme 31**, except using cyclobutanone in **step 4**:

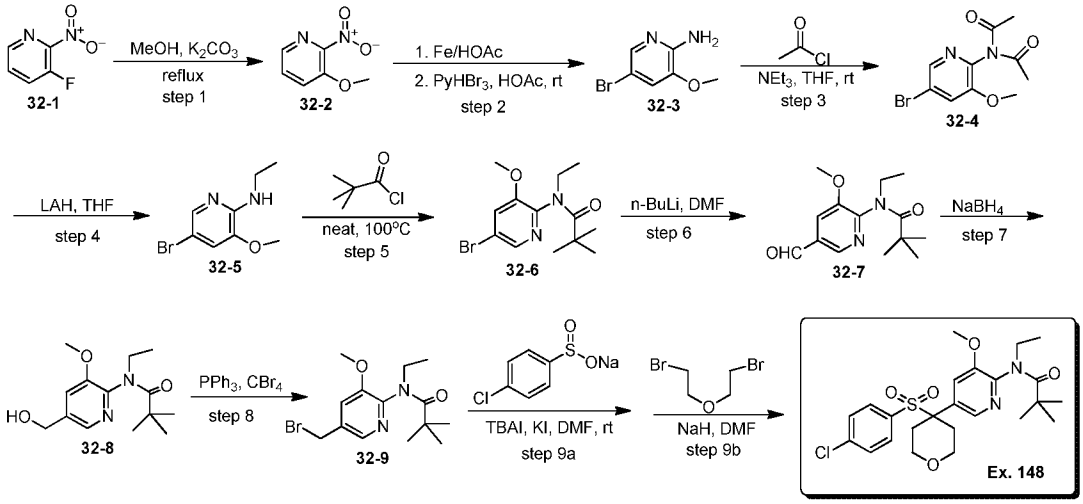
[00581] ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 4H), 7.24 – 7.08 (m, 3H), 4.87 – 4.76 (m, 1H), 4.01 – 3.97 (m, 2H), 3.34 – 3.26 (m, 2H), 2.65 – 2.55 (m, 2H) 2.40 – 2.31 (m, 2H), 2.10 – 2.05 (m, 2H), 1.65 – 1.53 (m, 4H), 1.07 (s, 9H). LC-MS: m/z = 508.1 $[M+H]^+$.

[00582] Example #147: was prepared as described in **Scheme 31**, except the ethyl substituent was inserted in **step 5** using sodium hydride and ethyl iodide as outlined in **Scheme 10 step 1**

[00583] ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 4H), 7.23 – 7.11 (m, 3H), 4.03 – 3.94 (m, 2H), 3.57 – 3.47 (m, 2H), 3.29 (t, *J* = 11.6 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.41 – 2.32 (m, 2H), 1.09 – 0.98 (m, 12H). LC-MS: m/z = 482.1 $[M+H]^+$.

[00584] PREPARATIVE EXAMPLE #148.

[00585] Scheme 32.



[00586] Step 1: A mixture of 3-fluoro-2-nitropyridine (3 g, 21.1 mmol) and K_2CO_3 (5.8 g, mmol) in MeOH (30 mL) was refluxed for 1h and then cooled to room temperature. The mixture was filtered and the filtrate evaporated to give crude **32-2** as a yellow oil. LC-MS: m/z = 155.1 $[M+H]^+$.

[00587] Step 2: A mixture of compound **32-2** (3.2 g, 20.6 mmol), Fe (5.8 g, 130.2 mmol) and AcOH (30 mL) was stirred at room temperature for 1h. The mixture was filtered and to the filtrate was added $Py{\cdot}HBr{\cdot}Br_2$. The reaction stirred at room temperature overnight. Solvent was evaporated and the residue diluted with CH_3OH. The mixture was basified to pH 7 with $NaHCO_3$ and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 2/1) to give **32-3** as a yellow oil. LC-MS: m/z = 203.0 $[M+H]^+$.

[00588] Step 3: To a solution of **32-3** (1 g, 4.95 mmol) and TEA (1.5 g, 14.9 mmol) in dry THF (50 mL) acetyl chloride (0.78 g, 19.9 mmol) was slowly added at room temperature. The mixture was stirred overnight then washed with water and brine. The residue was dried over Na_2SO_4, filtered and evaporated to give **32-4** as a yellow oil. LC-MS: m/z = 286.9 $[M+H]^+$.

[00589] Step 4: $LiAlH_4$ (470 mg, 12.2 mmol) was added at room temperature to a solution of **1-4** (1.4 mg, 4.9 mmol) in THF (30 mL) and the solution stirred for 2h. The reaction was quenched with water and 10% NaOH aqueous solution. The resulting mixture was filtered and the filtrate evaporated to give **32-5** as a colorless oil. LC-MS: m/z = 230.9 $[M+H]^+$.

[00590] Step 5: A mixture of Compound **32-5** (0.48 g, 2.09 mmol) and pivaloyl chloride (20 mL) was stirred at 100°C overnight. The solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 8/1) to give **32-6** as a yellow oil. LC-MS: m/z = 315.1 $[M+H]^+$.

[00591] Step 6: To a solution of compound **32-6** (0.23 g, 0.73 mmol) in THF (20 mL) nBuLi was added (0.5 mL, 1.1 mmol) at -78°C and the reaction stirred for 5 mins. DMF (0.11 g, 1.46 mmol) was added and stirred for 10 min. The reaction was quenched with water and the resulting mixture was filtered and the filtrate evaporated to give crude **32-7** as a yellow oil. LC-MS: m/z = 265.1 $[M+H]^+$.

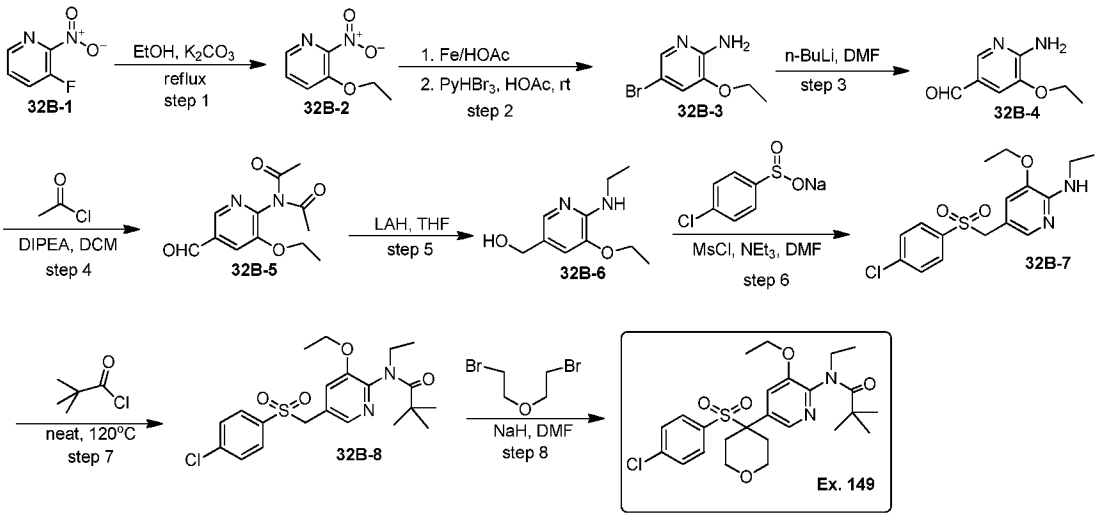
[00592] Step 7: A mixture of crude **32-7** (0.18 g, 0.68 mmol) and $NaBH_4$ (0.078 g, 2.05 mmol) in MeOH (10 mL) was stirred at room temperature for 1 h. The solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 1/1) to give **32-8** as a colorless oil. LC-MS: m/z = 267.1 $[M+H]^+$.

[00593] Step 8: To a solution of compound **32-8** (80 mg, 0.3 mmol) and CBr_4 (105 mg, 0.32 mmol) in CH_2Cl_2 (5 mL), PPh_3 (83 mg, 0.32 mmol) was added at room temperature and stirred for 10 min. The reaction was evaporated and the residue purified by column chromatography (eluent: PE/EA = 3/1) to give **32-9** as a colorless oil. LC-MS: m/z = 328.9 $[M+H]^+$.

[00594] Step 9: A mixture of compound **32-9** (160 mg, 0.49 mmol), sodium 4-chlorobenzenesulfinate (0.15 g, 0.73 mmol), TBAI (36 mg, 0.1 mmol) and KI (11 mg, 0.1 mmol) in DMF (10 mL) was stirred at room temperature for 1 h. NaH (59 mg, 2.44 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (0.34 g, 1.46 mmol) were added. The resulting reaction was stirred at room temperature for another 3 h. The reaction was quenched with water and extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 1/1) to give **Example #148** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.60 (m, 1H), 7.39 – 7.29 (m, 5H), 4.05 – 4.01 (m, 2H), 3.85 – 3.50 (m, 5H), 3.33 (t, *J* = 11.7 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.40 – 2.36 (m, 2H), 1.12 – 1.05 (m, 12H). LC-MS: m/z = 495.2 $[M+H]^+$.

[00595] PREPARATIVE EXAMPLE #149.

[00596] Scheme 32B.



[00597] Step 1: The reaction mixture of 3-fluoro-2-nitropyridine (5 g, 35.2 mmol), K_2CO_3 (9.72 g, mmol) and C_2H_5OH (50 mL) was refluxed for 2h and then the mixture was cooled to room temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1) to give **32B-2** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H), 7.53-7.46 (m, 2H), 4.20 (q, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H). LC-MS: m/z = 169.1 $[M+H]^+$.

[00598] Step 2: The reaction mixture of **32B-2** (5.5 g, 32.7 mmol), Fe (9.2 g, 163.7 mmol) and AcOH (200 Ml) was stirred at room temperature for 1h. Then the mixture was filtered and to the filtrate was added $Py{\cdot}HBr{\cdot}Br_2$. The mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was dissolved in CH_3OH. The mixture was basified with ammonia water and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 7/1 to 5/1) to give **32B-3** as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 1.9 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 4.85 (s, 2H), 4.03 (q, J = 7.0 Hz, 2H), 1.45 (t, J = 7.0 Hz, 3H). LC-MS: m/z = 216.9, 218.9 $[M+H]^+$.

[00599] Step 3: nBuLi (18 mL, 45.9 mmol) was added to a -78°C solution of compound **32B-3** (1.66 g, 7.64 mmol) and THF (50 mL) under N_2 and the reaction stirred for 30 mins. DMF (1.12 g, 15.3 mmol) was added and stirred for 2h. After completion, the reaction was quenched with water. The resulting mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1 to 3/1) to give **32B-4** as a yellow solid. LC-MS: m/z = 167.0 $[M+H]^+$.

[00600] Step 4: To the solution of **32B-4** (810 mg, 4.87 mmol), DIPEA (3.14 g, 24.4 mmol) and CH_2Cl_2 (20 mL) was added acetyl chloride (1.15 g, 14.61 mmol) slowly at 0°C and stirred for 2h. The mixture was washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1 to 3/1) to give **32B-5** as a yellow solid. LC-MS: m/z = 251.0 $[M+H]^+$.

[00601] Step 5: $LiAlH_4$ (461 mg, 12.15 mmol) was added to a 0°C solution of **32B-5** (0.76 mg, 3.04 mmol) and THF (30 mL) under N_2 and stirred for 3h. The reaction was quenched with water and 10% NaOH aqueous solution. The resulting mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH = 50/1) to give **32B-6** as a colorless oil. LC-MS: m/z = 197.2 $[M+H]^+$.

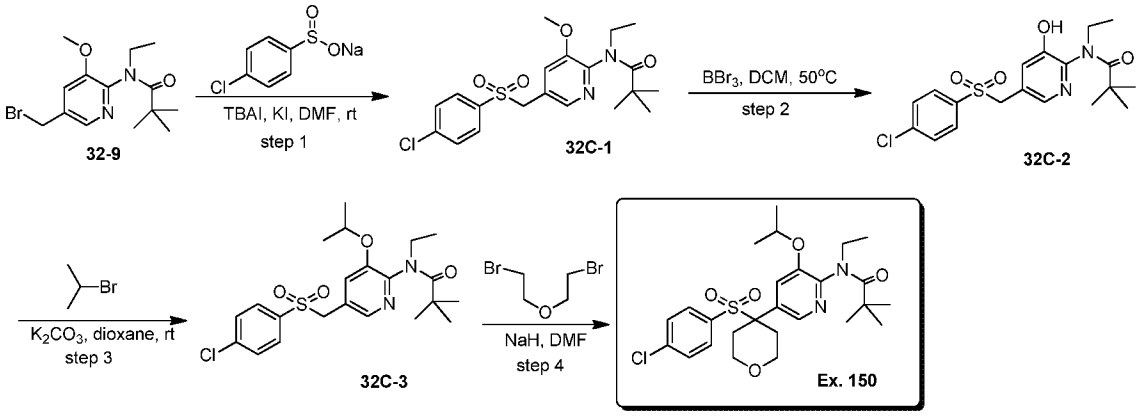
[00602] Step 6: The reaction of **32B-6** (150 mg, 0.76 mmol), sodium 4-chlorobenzenesulfinate (152 mg, 0.76 mmol), Et_3N (230 g, 2.28 mmol), methylsulfonyl chloride (104 mg, 0.91 mmol) and DMF (5 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 3/1) to give **32B-7** as a yellow gum. LC-MS: m/z = 354.9 $[M+H]^+$.

[00603] Step 7: The mixture of **32B-7** (46 mg, 0.13 mmol) and pivaloyl chloride (5 mL) was stirred at 130°C for 2h. The solvent was evaporated and the residue purified by prep-TLC (eluent: PE/EA = 2/1) to give **32B-8** as a colorless gum. LC-MS: m/z = 438.9 $[M+H]^+$.

[00604] Step 8: To the solution of compound **32B-8** (30+48 mg, 0.068+0.11 mmol) in dry DMF (5 mL) was added NaH (14+22 mg, 0.34+0.55 mmol) and 2,2'-dibromodiethyl ether (48+76 mg, 0.21+0.33 mmol) at 0°C and then stirred at the same temperature for 1h. Water was added and the resulting mixture was extracted with EA (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by prep-TLC (eluent: CH_2Cl_2/CH_3OH = 250/4) to give **Example #149** as a colorless gum. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.37-7.26 (m, 5H), 4.07-3.99 (m, 4H), 3.65 (s, 2H), 3.35-3.27 (m, 2H), 2.64-2.59 (m, 2H), 2.35 (d, J = 13.8 Hz, 2H), 1.43 (t, J = 6.9 Hz, 3H), 1.11-1.04 (m, 12H). LC-MS: m/z = 509.1 $[M+H]^+$.

[00605] PREPARATIVE EXAMPLE #150.

[00606] Scheme 32C.



[00607] Step 1: mixture of compound **32-9** (0.44 g, 1.34 mmol), sodium 4-chlorobenzenesulfinate (0.4 g, 2.01 mmol), TBAI (0.1 g, 0.27 mmol) and KI (31 mg, 0.27 mmol) in DMF (20 mL) was stirred at room temperature for 1 h. The reaction was quenched with water and extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 1/1) to give the **32C-1** as a yellow oil. LC-MS: m/z = 424.9 $[M+H]^+$.

[00608] Step 2: A mixture of compound **32C-1** (0.2 g, 0.47 mmol), BBr_3 (0.59 g, 2.36 mmol) and DCM (20 mL) was stirred at 40°C overnight. The reaction was quenched with water, basified with $NaHCO_3$, and extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give **32C-2** as a colorless oil. LC-MS: m/z = 411.0 $[M+H]^+$.

[00609] Step 3: A mixture of **32C-2** (0.15 g, 0.37 mmol), 2-bromopropane (0.067 g, 0.55 mmol) and K_2CO_3 (0.1 g, 0.73 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction was quenched with water and extracted with EA (20 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give crude **32C-3** as a yellow oil. LC-MS: m/z = 453.0 $[M+H]^+$.

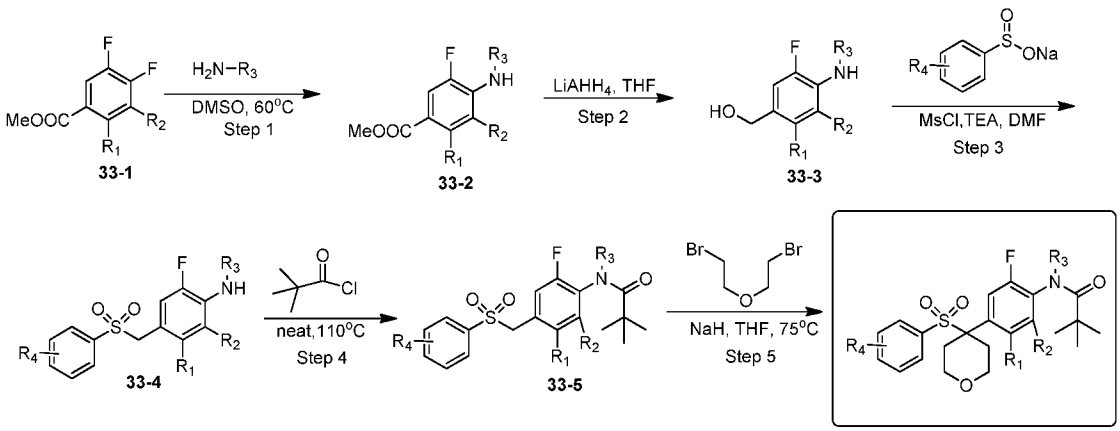
[00610] Step 4: To a solution of **32C-3** (140 mg, 0.31 mmol) in dry DMF (10 mL) was added NaH (23 mg, 0.93 mmol) and 2,2'-dibromodiethyl ether (150 mg, 0.62 mmol) at room temperature and then stirred for 3h. Water was added and the resulting mixture was extracted with EA (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by prep-TLC (eluent: PE/EA = 1/1) to give Example # 150 as a

white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.38 – 7.30 (m, 5H), 4.61 – 4.53 (m, 1H), 4.05 – 3.99 (m, 2H), 4.73 – 3.60 (m, 2H), 3.33 (t, *J* = 11.7 Hz, 2H), 2.71 – 2.62 (m, 2H), 2.39 – 2.31 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.16 – 1.03 (m, 12H). LC-MS: m/z = 523.2 $[M+H]^+$.

[00611] Example #151: was prepared as described in **Scheme 32C,** using (bromomethyl)cyclopropane in **step 3**. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.60 (s, 1H), 7.38 – 7.30 (m, 5H), 4.04 – 3.98 (m, 2H), 3.83 – 3.64 (m, 4H), 3.32 (t, *J* = 11.5 Hz, 2H), 2.71 – 2.60 (m, 2H), 2.39 – 2.31 (m, 2H), 1.32 – 0.96 (m, 13H), 0.71 – 0.65 (m, 2H), 0.40 – 0.36 (m, 2H). LC-MS: m/z = 535.2 $[M+H]^+$.

[00612] PREPARATIVE EXAMPLE #152

[00613] Scheme 33.



[00614] Step 1: A mixture of **33-1** (R_1, R_2 = H) (2.4 g, 14 mmol) and cyclobutanamine (2 g, 28 mmol) in DMSO (30 mL) was stirred at 60 °C for 12 hrs. The reaction was poured into ice water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. After being concentrated, the crude product was purified by flash column chromatography eluting with PE/EA = 10/1 to give **33-2** as a white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 - 7.68 (m, 1H), 7.63 - 7.58 (m, 1H), 6.60 - 6.54 (m, 1H), 4.01 - 3.96 (m, 1H), 3.85 (s, 3H), 2.48 - 2.42 (m, 2H), 1.97 - 1.83 (m, 4H). LC-MS: m/z = 224.1 $[M+H]^+$.

[00615] Step 2: LAH (0.72 g, 18.8 mmol) was added to a mixture of **33-2** (2.1 g, 9.4 mmol) in THF (120 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with H_2O (3 mL) and filtered. The filtrate was concentrated to give crude **33-3** as a yellow oil. LC-MS: m/z = 196.1 $[M+H]^+$.

[00616] Step 3: To a mixture of **33-3** (1.2 g, 6.1 mmol), sodium 4-chlorobenzenesulfinate (1.33 g, 6.7 mmol) and TEA (1.85 g, 18.3 mmol) in DMF (50 mL) was added methanesulfonyl chloride (1.05 g, 9.2 mmol) at 0 °C. The mixture was stirred at room temperature for 2 hours. Water (40 mL) was added and the mixture extracted with EtOAc (40 mL x 2). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography to give the product **33-4** as a yellow solid. LC-MS: m/z = 353.9 $[M+H]^+$.

[00617] Step 4: A mixture of compound of **33-4** (0.3 g, 0.85 mmol) and pivaloyl chloride (10 mL) was stirred at 110 °C for 4 hours. After removed of most of pivaloyl chloride, water (20 mL) was added. The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to give **33-5** as a yellow solid. LC-MS: m/z = 438.1 $[M+H]^+$.

[00618] Step 5: To a mixture of compound **33-5** (0.25 g, 0.58 mmol) and NaH (47 mg, 1.16 mmol) in THF (20 mL) was added 1-(2-bromoethoxy)-2-bromoethane (202 mg, 0.87 mmol) at rt. The resulting mixture was stirred at 75°C for 6 hours, then quenched with H_2O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by preparative TLC to give **Example #152** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 4H), 7.12 – 7.01 (m, 3H), 4.84 – 4.77 (m, 1H), 4.02 (d, *J* = 10.8 Hz, 2H), 3.30 (t, *J* = 11.4 Hz, 2H), 2.78 – 2.57 (m, 2H), 2.35 (d, *J* = 13.2 Hz, 2H), 2.13 (d, *J* = 6.3 Hz, 2H), 1.67 – 1.56 (m, 4H), 1.07 (s, 9H). LC-MS: m/z = 508.1 $[M+H]^+$.

[00619] Example #153: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.13 (m, 5H), 6.86 (d, *J* = 8.6 Hz, 1H), 4.61 (s, 1H), 3.98 (d, *J* = 18.4 Hz, 5H), 3.27 (t, *J* = 11.1 Hz, 2H), 2.64 (t, *J* = 10.6 Hz, 2H), 2.35 (d, *J* = 13.8 Hz, 2H), 1.17 - 1.06 (m, 15H). LC-MS: m/z = 542.1 $[M+H]^+$.

[00620] Example #154: was prepared as described in **Scheme 33**, using ethylamine in **step 1**. ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.33 (s, 4H), 7.19-7.13 (m, 1H), 7.08-6.98 (m, 2H), 4.01-3.96 (m, 2H), 3.61 (br, 2H), 3.29-3.28 (m, 2H), 2.63-2.62 (m, 2H), 2.36-2.32 (m, 2H) 1.08 (br, 12H). LC-MS: m/z = 482.0 $[M+H]^+$.

[00621] Example #155: was prepared as described in **Scheme 33**, using tert-butylamine in **step 1**. ^1H NMR (300 MHz, CDCl3) δ 7.34 – 7.32 (m, 3H), 7.15-6.96 (m, 4H), 4.03-3.99 (m, 2H), 3.29-3.22 (m, 2H), 2.67-2.64 (m, 2H), 2.35-2.33 (m, 2H), 1.34 (s, 9H), 0.97 (s, 9H). LC-MS: m/z = 510.2 $[M+H]^+$.

[00622] Example #156: was prepared as described in **Scheme 33**, using 2-

methoxyethanamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 7.06 (dd, J = 11.4, 2.2 Hz, 1H), 6.96 (dd, J = 8.4, 2.1 Hz, 1H), 4.00 (d, J = 11.6 Hz, 2H), 3.75 (s, 2H), 3.54 (t, J = 5.2 Hz, 2H), 3.34-3.22 (m, 5H), 2.70-2.60 (m, 2H), 2.34 (d, J = 13.8 Hz, 2H), 1.08 (s, 9H). LC-MS: m/z = 511.9 $[M+H]^+$.

[00623] Example #157: was prepared as described in **Scheme 33**, using N^1-N^1-dimethylethane-1,2-diamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 7.08 (d, J = 11.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.00 (d, J = 10.2 Hz, 2H), 3.70 (s, 2H), 3.29 (t, J = 11.6 Hz, 2H), 2.65 (td, J = 13.5, 4.2 Hz, 2H), 2.49 (t, J = 7.3 Hz, 2H), 2.34 (d, J = 14.0 Hz, 2H), 2.26 (s, 6H), 1.08 (s, 9H). LC-MS: m/z = 525.1 $[M+H]^+$.

[00624] Example #158: was prepared as described in **Scheme 33**, using 1-methoxypropan-2-amine in **step 1**. ^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.35 (s, 1H), 7.31-7.27 (m, 1H), 7.18 (s, 1H), 5.04 (s, 1H), 3.99 (d, J = 11.4 Hz, 2H), 3.33-3.25 (m, 7H), 2.59-2.56 (m, 4H), 1.07 (s, 9H), 0.98 (s, 3H).). LC-MS: m/z = 525.9 $[M+H]^+$.

[00625] Example #159: was prepared as described in **Scheme 33**, using N^1-N^1-dimethylpropane-1,2-diamine in **step 1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.30 (s, 5H), 7.07 (d, J = 11.3 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.09 (s, 1H), 4.01 (d, J = 11.4 Hz, 2H), 3.28 (t, J = 11.7 Hz, 2H), 2.67 (t, J = 12.2 Hz, 2H), 2.38-2.02 (m, 10H), 1.04 (s, 9H), 0.96 (s, 3H). LC-MS: m/z = 539.2 $[M+H]^+$.

[00626] Example #160: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and cyclobutanecarbonyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 4H), 7.06-7.04 (m, 3H), 4.99 (s, 1H), 4.03-4.00 (m, 2H), 3.37-3.29 (m, 2H), 2.77-2.66 (m, 3H), 2.35-2.13 (m, 6H), 1.75-1.56 (m, 8H). LC-MS: m/z = 506.0 $[M+H]^+$.

[00627] Example #161: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and cyclohexanecarbonyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 4H), 7.13 – 7.07 (m, 3H), 5.01 – 4.98 (m, 1H), 4.05 – 4.02 (m, 2H), 3.33 – 3.27 (m, 2H), 2.71 – 2.64 (m, 3H), 2.34 – 2.16 (m, 4H), 1.86 – 0.94 (m, 15H). LC-MS: m/z = 534.1 $[M+H]^+$.

[00628] Example #162: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and 3-fluorobenzoyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 6.90 (m, 11H), 5.01 – 4.92 (m, 1H), 3.96 – 3.93 (m, 2H), 3.16 – 3.10 (m, 2H), 2.58 – 2.55 (m, 3H), 2.23 – 2.15 (m, 4H), 1.66 – 1.60 (m, 4H). LC-MS: m/z = 546.1 $[M+H]^+$.

[00629] Example #163: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and cyclopentanecarbonyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.13 – 7.04 (m, 3H), 5.05 – 4.98 (m, 1H), 4.05 – 4.01 (m, 2H), 3.35 (t, *J* = 11.3 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.35 – 2.13 (m, 5H), 2.84 – 1.42 (m, 12H). LC-MS: m/z = 520.1 $[M+H]^+$.

[00630] Example #164: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and acetyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.15 – 7.04 (m, 3H), 5.08 – 4.99 (m, 1H), 4.04 – 4.00 (m, 2H), 3.34 (t, *J* = 11.5 Hz, 2H), 2.71 – 2.61 (m, 2H), 2.39 – 2.04 (m, 5H), 1.80 – 1.58 (m, 7H). LC-MS: m/z = 466.1 $[M+H]^+$.

[00631] Example #165: was prepared as described in **Scheme 33**, using cyclobutylamine in **step 1** and cyclopropanecarbonyl chloride in **step 4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.20 – 7.08 (m, 3H), 5.05 – 4.96 (m, 1H), 4.04 – 4.01 (m, 2H), 3.36 (t, *J* = 11.5 Hz, 2H), 2.69 – 2.62 (m, 2H), 2.41 – 2.36 (m, 2H), 2.26 – 2.14 (m, 2H), 1.79 – 1.55 (m, 4H), 1.03 (s, 3H), 0.73 – 0.57 (m, 2H). LC-MS: m/z = 492.1 $[M+H]^+$.

[00632] Example #166: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using ethylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.38 (s, 4H), 6.89-6.86 (m, 2H), 4.02-3.99 (m, 2H), 3.63 (br, 2H), 3.33-3.25 (m, 2H), 2.63-2.61 (m, 2H), 2.31-2.27 (m, 2H) 1.12 – 1.10 (m, 12H). LC-MS: m/z = 500.1 $[M+H]^+$.

[00633] Example #167: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using cyclopropylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.38 – 7.37 (m, 4H), 6.87-6.85 (m, 2H), 4.03 - 3.97 (m, 2H), 3.34-3.26 (m, 2H), 3.16 (s, 1H), 2.67-2.64 (m, 2H), 2.33-2.27 (m, 2H), 1.26 (br, 9H), 0.83 (br, 2H), 0.56 (br, 2H). LC-MS: m/z = 512.2 $[M+H]^+$.

[00634] Example #168: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using cyclobutylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.38 (s, 4H), 6.91-6.88 (m, 2H), 4.79 (s, 1H), 4.05-4.01 (m, 2H), 3.34-3.24 (m, 2H), 2.67-2.64 (m, 2H), 2.33-2.31 (m, 2H), 2.28 (br, 2H), 1.61 (br, 4H), 1.07 (br, 9H). LC-MS: m/z = 526.1 $[M+H]^+$.

[00635] Example #169: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using tert-butylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.37 (s, 4H), 6.86 - 6.83 (m, 2H), 4.03 - 3.99 (m, 2H), 3.28 - 3.21 (m, 2H), 2.66 - 2.62 (m, 2H), 2.30 - 2.26 (m, 2H), 1.36 (s, 9H), 0.99 (s, 9H). LC-MS: m/z = 528.2 $[M+H]^+$.

[00636] Example #170: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using 1-methoxypropan-2-amine in **step 1.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (m, 4H),

6.93 (d, *J* = 10.6 Hz, 1H), 6.84 (d, *J* = 10.4 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.04 (d, *J* = 11.8 Hz, 2H), 3.53 (dd, *J* = 9.4, 4.6 Hz, 1H), 3.37-3.27 (m, 6H), 2.71-2.64 (m, 2H), 2.30 (t, *J* = 15.2 Hz, 2H), 1.14-1.08 (m, 12H). LC-MS: m/z = 543.9 $[M+H]^+$.

[00637] Example #171: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using cyclopropylmethanamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 4H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.01 (d, *J* = 10.1 Hz, 2H), 3.49 (s, 2H), 3.26 (t, *J* = 11.7 Hz, 2H), 2.64 (td, *J* = 13.7, 4.1 Hz, 2H), 2.29 (d, *J* = 13.5 Hz, 2H), 1.11 (s, 9H), 0.96-0.90 (m, 1H), 0.38 (d, *J* = 7.6 Hz, 2H), -0.05 (d, *J* = 4.8 Hz, 2H). LC-MS: m/z = 526.1 $[M+H]^+$.

[00638] Example # 172: was prepared as described in **Scheme 33**, with R_2 being Fluoro and using propan-2-amine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 4H), 6.87-6.848 (m, 2H), 4.83 (br, 1H), 4.02-3.99 (m, 2H), 3.31-3.23 (m, 2H), 2.65-2.63 (m, 2H), 2.31-2.26 (m, 2H) 1.04 (br, 15H). LC-MS: m/z = 514.1 $[M+H]^+$.

[00639] Example # 173: was prepared as described in **Scheme 33**, with R_1 being Fluoro and using cyclobutylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.35 (m, 4H), 7.24-7.18 (m, 1H), 6.75 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.81-4.73 (m, 1H), 4.09-4.03 (m, 2H), 3.31 (t, *J* = 12.5 Hz, 2H), 2.56 (s, 4H), 2.16-2.14 (m, 2H), 1.63-1.60 (m, 4H), 1.11 (s, 9H). LC-MS: m/z = 526.1 $[M+H]^+$.

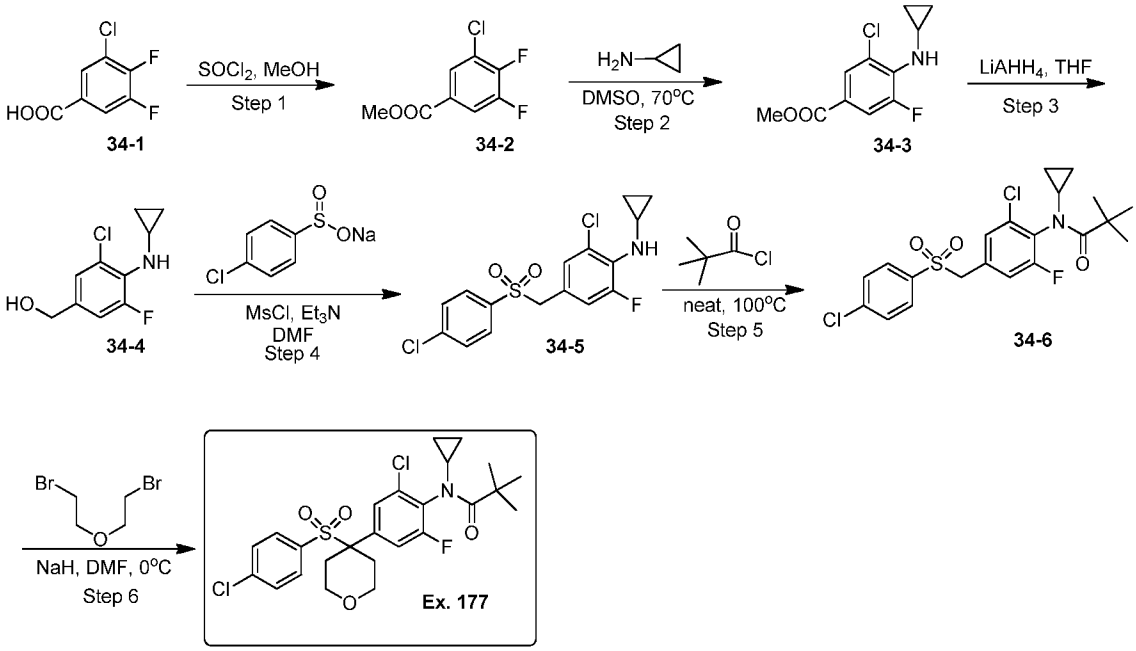
[00640] Example # 174: was prepared as described in **Scheme 33**, with R_1 being Fluoro and using propan-2-amine in **step 1.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (q, *J* = 8.8 Hz, 4H), 7.23 (dd, *J* = 10.9, 7.1 Hz, 1H), 6.77 (dd, *J* = 12.7, 6.5 Hz, 1H), 4.90 (dt, *J* = 13.4, 6.7 Hz, 1H), 4.08 (dt, *J* = 11.8, 3.1 Hz, 2H), 3.33 (t, *J* = 12.6 Hz, 2H), 2.60-2.58 (m, 4H), 1.14 (s, 9H), 1.08 (d, *J* = 6.6 Hz, 6H). LC-MS: m/z = 513.9 $[M+H]^+$.

[00641] Example #175: was prepared as described in **Scheme 33**, with R_1 being Fluoro and using cyclopropylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 4H), 7.18 (dd, *J* = 10.7, 7.0 Hz, 1H), 6.71 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.32 (t, *J* = 12.3 Hz, 2H), 3.10-3.08 (m, 1H), 2.56 (s, 4H), 1.18 (s, 9H), 0.86-0.84 (m, 2H), 0.53 (s, 2H). LC-MS: m/z = 583.2 $[M+H]^+$.

[00642] Example #176: was prepared as described in **Scheme 33**, with R_1 being Fluoro and using tert-butylamine in **step 1.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.37 (m, 4H), 7.18 (dd, *J* = 10.8, 7.2 Hz, 1H), 6.77 (dd, *J* = 12.6, 6.6 Hz, 1H), 4.05 (d, *J* = 11.8 Hz, 2H), 3.27 (t, *J* = 10.8 Hz, 2H), 2.55 (s, 4H), 1.34 (s, 9H), 0.99 (s, 9H). LC-MS: m/z = 472.1 $[M+H]^+$.

[00643] PREPARATIVE EXAMPLE #177

[00644] Scheme 34.



[00645] Step 1: A reaction mixture of **34-1** (3.5 g, 18.2 mmol) and $SOCl_2$ (2.17 g, 18.2 mmol) in CH_3OH (50 mL) was stirred at 50°C for 3 hrs. The solvent was evaporated and the resulting residue was purified by column chromatography (eluent: PE/EA = 10/1) to give **34-2** as a colorless oil. LC-MS: m/z = 207.5 $[M+H]^+$.

[00646] Step 2: A reaction mixture of **34-2** (1.1 g, 5.32 mmol) and cyclopropanamine (608 mg, 10.65 mmol) in DMSO (10 mL) was stirred at 70°C overnight. Water was added and the resulting mixture was extracted with EA (30 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE to PE/EA = 10/1) to give **34-3** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, J = 1.9, 1.3 Hz, 1H), 7.58 (dd, J = 13.1, 1.9 Hz, 1H), 4.68 (s, 1H), 3.86 (s, 3H), 3.02-2.94 (m, 1H), 0.82-0.76 (m, 2H), 0.62-0.59 (m, 2H). LC-MS: m/z = 244.1 $[M+H]^+$.

[00647] Step 3: $LiAlH_4$ (393 mg, 10.34 mmol) was added to a 0°C solution of **34-3** (1.26 g, 5.17 mmol) in THF (30 mL) under N_2 and stirred for 2h. The reaction was quenched with water and 10% NaOH aqueous solution. The resulting mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH = 10/1 to 6/1) to give **34-4** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.05-7.04 (m, 1H), 6.94 (dd, J = 12.6, 1.9 Hz, 1H), 4.52 (s, 2H), 2.92-2.84 (m, 1H), 0.75-0.69 (m, 2H), 0.59-0.53

(m, 2H). LC-MS: m/z = 216.1 $[M+H]^+$.

[00648] **Step 4:** A mixture of **34-4** (960 mg, 4.45 mmol), sodium 4-chlorobenzenesulfinate (1.06 g, 5.34 mmol) and Et_3N (1.35 g, 13.35 mmol) in DMF (10 mL) was stirred at room temperature overnight. Water was added and the mixture extracted with EA (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE.EA = 25/1 to 12/1) to give **34-5** as a brown gum. ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 6.77-6.71 (m, 2H), 4.30 (s, 1H), 4.13 (s, 2H), 2.89 (td, J = 6.7, 3.5 Hz, 1H), 0.75 (q, J = 6.6 Hz, 2H), 0.57 (s, 2H). LC-MS: m/z = 374.0 $[M+H]^+$.

[00649] **Step 5:** A mixture of **34-5** (310 mg, 0.83 mmol) and pivaloyl chloride (10 mL) was stirred at 100°C for 6h. Then the solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 6/1 to 2/1) to give **34-6** as a colorless gum. ^1H NMR (301 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.00 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.27 (s, 2H), 3.13 (s, 1H), 1.43-0.37 (m, 13H). LC-MS: m/z = 458.0 $[M+H]^+$.

[00650] **Step 6:** NaH (94 mg, 2.36 mmol) and 2,2'-dibromodiethyl ether (273 mg, 1.18 mmol) were added to a 0°C solution of **34-6** (270 mg, 0.59 mmol) in dry DMF (10 mL) and stirred for 1h. Water was added and the resulting mixture extracted with EA (30 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 8/1 to 1/1) to give **Example #177** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.32 (m, 4H), 7.03-6.95 (m, 2H), 4.00 (d, J = 10.9 Hz, 2H), 3.34-3.16 (m, 3H), 2.67-2.58 (m, 2H), 2.29 (d, J = 13.6 Hz, 2H), 1.47-0.65 (m, 13H). LC-MS: m/z = 528.1 $[M+H]^+$.

[00651] **Example #178:** was prepared as described in **Scheme 34**, but using ethylamine in **step 2.** ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 4H), 7.09 – 6.98 (m, 2H), 4.02 – 3.99 (m, 3H), 3.33 – 3.14 (m, 3H), 2.61 – 2.59 (m, 2H), 2.33 - 2.29 (m, 2H), 1.41 (br, 1H), 0.87 – 0.85 (m, 9H), 0.65 – 0.58 (m, 2H). LC-MS: m/z = 515.9 $[M+H]^+$.

[00652] **Example #179:** was prepared as described in **Scheme 34**, but using cyclobutylamine in **step 2.** ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.03 – 6.97 (m, 2H), 4.67 (br, 1H), 4.01 – 3.97 (m, 2H), 3.28 – 3.21 (m, 2H), 2.62 - 2.59 (m, 2H), 2.35 - 2.28 (m, 2H), 2.15 (br, 1H), 1.57 (br, 4H), 1.39 (br, 2H),1.01 (br, 7H). LC-MS: m/z = 542.1 $[M+H]^+$.

[00653] **Example #180:** was prepared as described in **Scheme 34**, but using cyclopropylmethanamine in **step 2.** ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.12 (s, 1H),

7.01 (d, *J* = 10.2 Hz, 1H), 4.04 (d, *J* = 10.0 Hz, 3H), 3.29 (s, 2H), 2.92 (s, 1H), 2.66 (s, 2H), 2.33 (d, *J* = 13.4 Hz, 2H), 1.51 (d, *J* = 42.3 Hz, 2H), 1.05 (d, *J* = 52.1 Hz, 8H), 0.40 (s, 2H), 0.09 (s, 1H), -0.14 (s, 1H). LC-MS: m/z = 542.1 $[M+H]^+$.

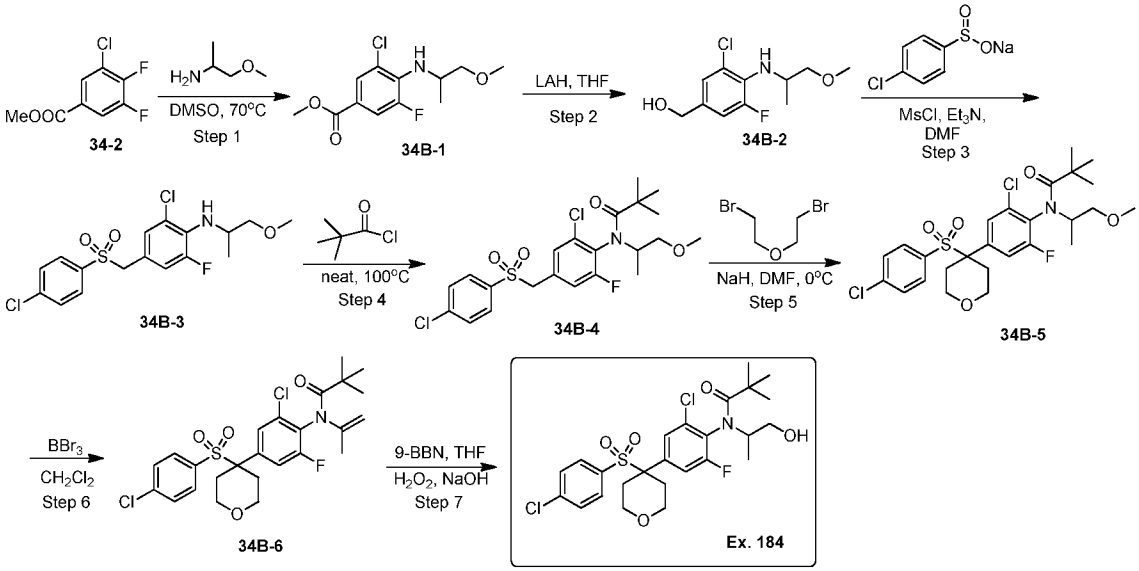
[00654] Example #181: was prepared as described in **Scheme 34**, but using (R)-1-cyclopropylethanamine in **step 2.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 4H), 7.10 (s, 1H), 7.00 (d, *J* = 10.5 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 2H), 3.62 (d, *J* = 57.0 Hz, 1H), 3.27 (t, *J* = 10.6 Hz, 2H), 2.66 (t, *J* = 11.1 Hz, 2H), 2.32 (d, *J* = 13.8 Hz, 2H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.08 (s, 9H), 0.78 (dd, *J* = 25.2, 21.5 Hz, 1H), 0.49-0.10 (m, 4H). LC-MS: m/z = 555.7 $[M+H]^+$.

[00655] Example #182: was prepared as described in **Scheme 34**, but using (S)-1-cyclopropylethanamine in **step 2.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 4H), 7.10 (s, 1H), 7.00 (d, *J* = 10.6 Hz, 1H), 4.04 (d, *J* = 11.1 Hz, 2H), 3.62 (d, *J* = 55.1 Hz, 1H), 3.27 (t, *J* = 10.4 Hz, 2H), 2.66 (t, *J* = 10.8 Hz, 2H), 2.32 (d, *J* = 13.6 Hz, 2H), 1.37 (d, *J* = 6.1 Hz, 3H), 1.09 (s, 9H), 0.81-0.70 (m, 1H), 0.49-0.12 (m, 4H). LC-MS: m/z = 555.7 $[M+H]^+$.

[00656] Example #183: was prepared as described in **Scheme 34**, but using propan-2-amine in **step 2.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.37 (m, 4H), 7.05 – 6.97 (m, 2H), 4.47 (br, 1H), 4.12 – 3.99 (m, 2H), 3.30 – 3.22 (m, 2H), 2.64 - 2.59 (m, 2H), 2.29 - 2.23 (m, 2H), 1.21 – 0.88 (m, 15H). LC-MS: m/z = 530.0 $[M+H]^+$.

[00657] PREPARATIVE EXAMPLE #184

[00658] Scheme 34B.



[00659] Step 1: A mixture of **34-2** (1.5 g, 7.26 mmol), 1-methoxypropan-2-amine (1.29 g, 14.5 mmol) and DMSO (10 mL) was stirred at 70°C overnight. Water was added and the resulting mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE to PE/EA = 100/1) to give **34B-1** as a colorless oil. ^{1}H NMR (301 MHz, $CDCl_3$) δ 7.75-7.74 (m, 1H), 7.54 (dd, *J* = 13.6, 1.9 Hz, 1H), 4.59 (s, 1H), 4.13-4.08 (m, 1H), 3.84 (s, 3H), 3.45-3.35 (m, 5H), 1.23 (d, *J* = 6.5 Hz, 3H). LC-MS: m/z = 276.0 $[M+H]^+$.

[00660] Step 2: $LiAlH_4$ (431 mg, 11.33 mmol) was added to a 0°C solution of **34B-1** (1.25 g, 4.53 mmol) and THF (40 mL) and stirred for 2h. The reaction was quenched with water and 10% NaOH aqueous solution. The resulting mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography (eluent: PE/EA = 8/1 to 4/1) to give **34B-2** as a colorless gum. ^{1}H NMR (301 MHz, $CDCl_3$) δ 7.06 (d, *J* = 0.5 Hz, 1H), 6.90 (dd, *J* = 12.7, 1.9 Hz, 1H), 4.52 (s, 2H), 3.90-3.84 (m, 1H), 3.37 (d, *J* = 4.1 Hz, 2H), 3.34 (s, 3H), 1.18 (dd, *J* = 6.5, 0.5 Hz, 3H). LC-MS: m/z = 248.0 $[M+H]^+$.

[00661] Step 3: A mixture of **34B-2** (800 mg, 3.23 mmol), sodium 4-chlorobenzenesulfinate (769 mg, 3.88 mmol), Et_3N (979 mg, 9.69 mmol), methylsulfonyl chloride (444 mg, 3.88 mmol) and DMF (10 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 10/1 to 8/1) to give **34B-3** as a colorless gum. ^{1}H NMR (301 MHz, CD_3OD) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.89 (s, 1H), 6.82 (d, *J* = 13.2 Hz, 1H), 4.42 (s, 2H), 3.91 (s, 1H), 3.40 (d, *J* = 4.4 Hz, 2H), 3.34 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H). LC-MS: m/z = 405.9 $[M+H]^+$.

[00662] Step 4: A mixture of **34B-3** (600 mg, 1.48 mmol) and pivaloyl chloride (10 mL) was stirred at 100°C overnight. The solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 8/1 to 3/1) to give **34B-4** as a colorless gum. LC-MS: m/z = 490.0 $[M+H]^+$.

[00663] Step 5: NaH (126 mg, 3.15 mmol) and 2,2'-dibromodiethyl ether (293 mg, 1.26 mmol) were added to a 0°C solution of compound **34B-4** (310 mg, 0.63 mmol) in dry DMF (5 mL) under N_2 and stirred for 30 min. Water was added and the resulting mixture was extracted with EA (30 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1 to

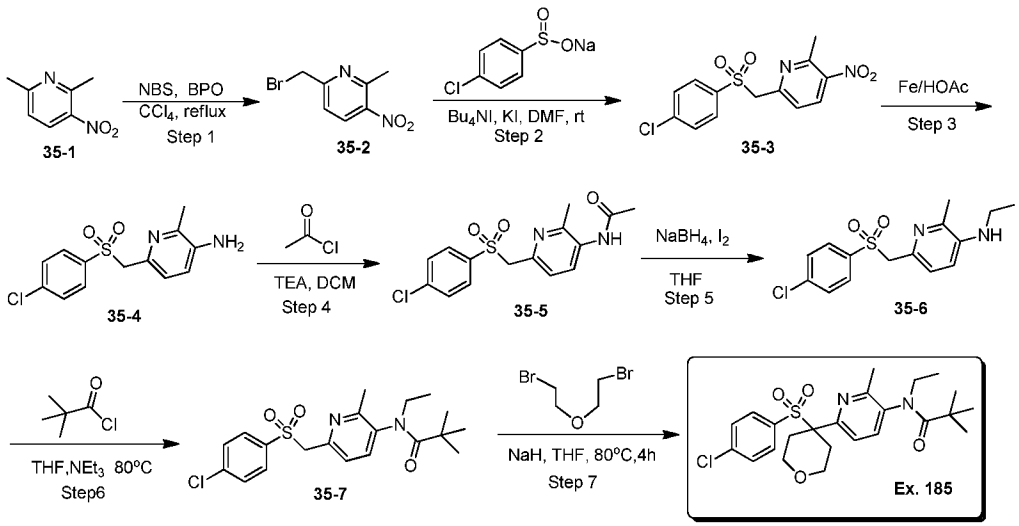
3/1) to give **34B-5** as a white solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.38 (m, 4H), 7.10-6.96 (m, 2H), 4.33-4.31 (m, 1H), 4.04 (d, *J* = 11.4 Hz, 2H), 3.71-3.54 (m, 2H), 3.35-3.29 (m, 5H), 2.70-2.62 (m, 2H), 2.34-2.29 (m, 2H), 1.45-1.17 (m, 4H), 1.7 (s, 8H). LC-MS: m/z = 560.1 $[M+H]^+$.

[00664] Step 6: BBr_3 (0.02 mL) was added to a solution of compound **34B-5** (60 mg, 0.11 mmol) and CH_2Cl_2 (5 mL) and stirred at room temperature for 1h. The mixture was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by prep-TLC(eluent: CH_2Cl_2/CH_3OH = 50/1) to give **34B-6** as a colorless gum. LC-MS: m/z = 527.7 $[M+H]^+$.

[00665] Step 7: 9-BBN was added to a solution of **34B-6** (15 mg, 0.028 mmol) in THF (5 mL) at 0°C and the mixture was stirred overnight. 3N NaOH (0.2 mL) and 30% H_2O_2 (0.2 mL) were added slowly to the reaction mixture at 0°C and then the mixture was stirred for 6h at room temperature. After being extracted with EA (10 mL x2), the organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (eluent: CH_2Cl_2/CH_3OH = 50/1) to give the impure product which was purified by prep-HPLC to give **Example #184** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 4H), 7.15-7.01 (m, 2H), 4.03 (d, J = 10.4 Hz, 2H), 3.94-3.83 (m, 3H), 3.30 (t, J = 11.8 Hz, 2H), 2.63 (t, J = 11.0 Hz, 2H), 2.33 (d, J = 13.4 Hz, 2H), 1.40 (d, J = 6.2 Hz, 1H), 1.28 (d, J = 6.7 Hz, 2H), 1.09 (s, 9H). LC-MS: m/z = 546.1 $[M+H]^+$.

[00666] PREPARATIVE EXAMPLE #185

[00667] Scheme 35.



[00668] **Step 1:** A mixture of **35-1** (6.1 g, 40 mmol), NBS (10.7 g, 60 mmol) and AIBN (1.3 g, 8 mmol) in CCl_4 (200 mL) was stirred overnight at 80°C. After concentration, the resulting mixture was purified by column chromatography, eluting with PE/EA = 20/1 to **35-2** as a yellow oil. LC-MS: m/z = 230.9 $[M+H]^+$.

[00669] **Step 2:** A solution of Sodium 4-chlorobenzenesulfinate (2.16 g, 10.92 mmol), **35-2** (2.1 g, 9.1 mmol), Bu_4NI (0.67 g, 1.82 mmol) and KI (0.3 g, 1.82 mmol) in DMF (60 mL) was stirred at 30 °C for 2 hrs. After filtration, the filtrate was concentrated. Water (100 mL) was added and the mixture extracted with EtOAc (60 mL x 2). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (PE/EA=3/1) to give **35-3** as a white solid. LC-MS: m/z = 326.8 $[M+H]^+$.

[00670] **Step 3:** : A mixture of **35-3** (1.6 g, 4.9 mmol) and iron powder (1.37 g, 24.5 mmol) in AcOH (80 mL) was stirred at r.t for 4 hrs. After filtration the filtrate was diluted with EA (100 mL x 2) and 1 N NaOH (60 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated to the crude product. The crude **35-4** was purified by column chromatography (PE/EA=1/1) to give **35-4** as a yellow solid. LC-MS: m/z = 296.9 $[M+H]^+$.

[00671] **Step 4:** Acetyl chloride (0.59 g, 0.75 mmol) was added slowly to a 0 °C solution of **35-4** (0.9 g, 0.31 mmol) and TEA (1.5 g, 14.9 mmol) in dry DCM (30 mL). After stirring at room temperature for 2 hrs, the mixture was washed with water and brine, dried over Na_2SO_4 and evaporated to give crude **35-5**. The crude product was purified by column chromatography (PE/EA=3/1) to give **35-5** as a yellow solid. LC-MS: m/z = 338.9 $[M+H]^+$.

[00672] **Step 5:** A mixture of **35-5** (0.334 g, 1 mmol), I_2 (0.758 g, 3 mmol) and $NaBH_4$ (0.114 g, 3 mmol) in THE (30 mL) was stirred at room temperature for 12 hrs. The reaction was quenched with H_2O (30 mL) and extracted with EA (30 mL x 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (PE/EA=2/1) to give **35-6** as a yellow solid. LC-MS: m/z = 324.9 $[M+H]^+$.

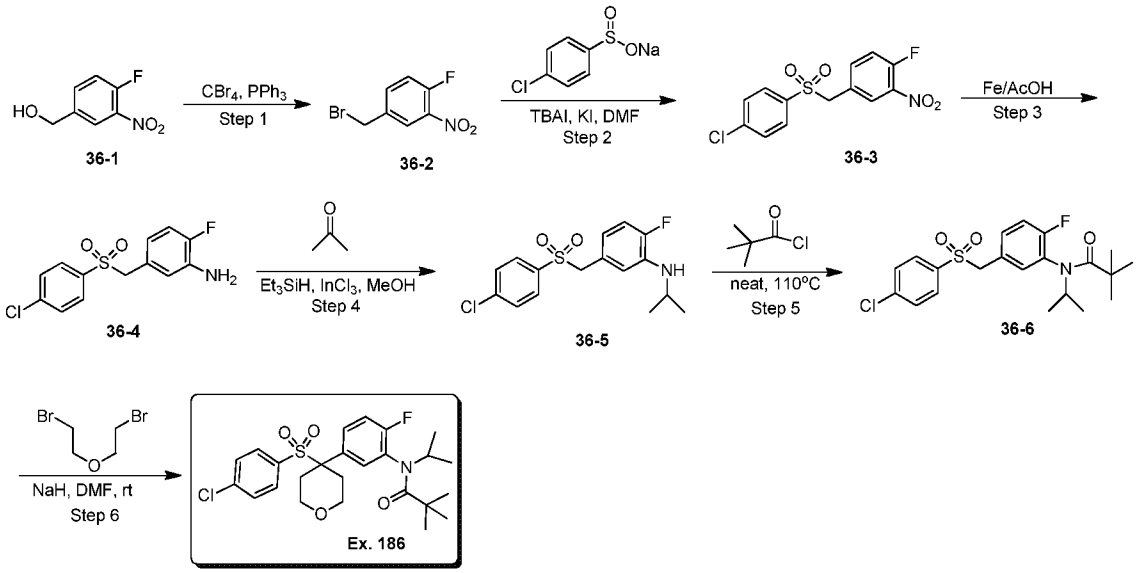
[00673] **Step 6:** A mixture of **35-6** (0.24 g, 0.75 mmol) and pivaloyl chloride (8 mL) was stirred at 110°C for 4 hrs. Solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 2/1) to give **35-7** as a yellow solid. LC-MS: m/z = 408.9 $[M+H]^+$.

[00674] **Step 7:** NaH (0.052 g, 1.28 mmol) and 2,2'-dibromodiethyl ether (0.22 g, 0.96 mmol) were added to a solution of **35-7** (0.26 g, 0.64 mmol) in dry THF (20 mL). The

resulting solution was stirred at 75°C for 4 hrs. Water was added and the mixture extracted with EA (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by prep-TLC (eluent: PE/EA = 1/1) to give **Example #185** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 1H), 7.46 - 7.43 (m, 1H), 7.32 - 7.24 (m, 4H), 4.17- 4.15 (m, 1H), 3.98 - 3.94 (m, 2H), 3.19 - 3.15 (m, 2H), 3.01 (br, 1H), 2.62 - 2.52 (m, 4H), 2.14 (s, 3H), 1.13 - 1.08 (m, 12H). LC-MS: m/z =479.1 $[M+H]^+$.

[00675] PREPARATIVE EXAMPLE #186

[00676] Scheme 36.



[00677] Step 1: PBr_3 (3.8 g, 14 mmol) was added dropwise to a 0°C solution of **36-1** (2 g, 11.7 mmol) in DCM (30 mL). The reaction was stirred at 0°C for 1 hr. The reaction was quenched with water (50 m L) and extracted with DCM (50 mL x 3). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 10/1) to give **36-2** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.11 – 8.07 (m, 1H), 7.69 – 7.64 (m, 1H), 7.31 – 7.25 (m, 1H), 4.48 (s, 2H).

[00678] Step 2: A mixture of **36-2** (0.5 g, 1.5 mmol), sodium 4-chlorobenzenesulfinate (0.36 g, 1.80 mmol), KI (49 mg, 0.3 mmol) and TBAI (110 mg, 0.3 mmol) in DMF (20 mL) was stirred at room temperature for 1h. Solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 2/1) to give **36-3** as a yellow oil. LC-MS: m/z = 351.9 $[M+Na]^+$.

[00679] Step 3: A mixture of **36-3** (0.64 g, 1.49 mmol) and iron powder (0.84 g, 14.9 mmol) in AcOH (30 mL) was stirred at room temperature overnight. Solvent was evaporated and the residue diluted with water (30 m L) and basified with $NaHCO_3$ to pH = 7. The mixture was extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give **36-4** as a yellow oil. LC-MS: m/z = 300.0 $[M+H]^+$.

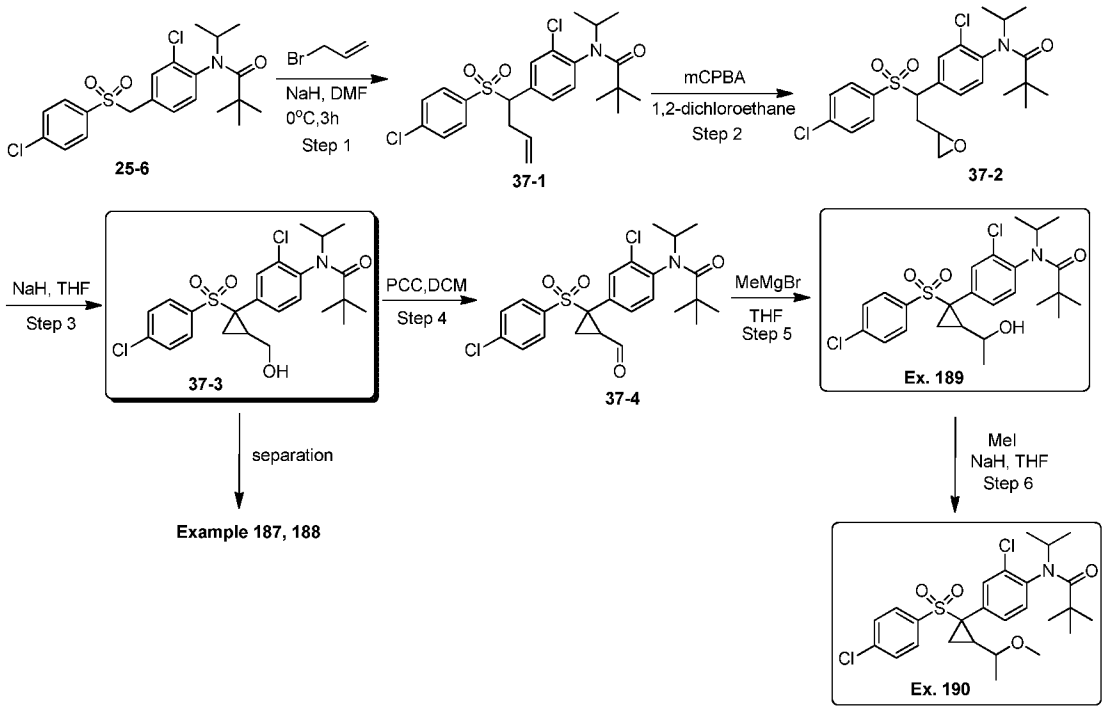
[00680] Step 4: A mixture of **36-4** (300 mg, 1 mmol), Et_3SiH (230 mg, 2 mmol), $InCl_3$ (67 mg, 0.3 mmol) and propan-2-one (120 mg, 2 mmol) in MeOH (100 mL) was stirred at room temperature overnight. The mixture was evaporated and the residue purified by column chromatography (eluent: PE/EA = 2/1) to give **36-5** as a yellow oil. LC-MS: m/z = 341.9 $[M+H]^+$.

[00681] Step 5: A mixture of **36-5** (200 mg, 0.59 mmol) and pivaloyl chloride (20 mL) was stirred at 110°C overnight. Solvent was evaporated and the residue purified by column chromatography (eluent: PE/EA = 1/1) to give **36-6** as a yellow oil. LC-MS: m/z = 425.9 $[M+H]^+$.

[00682] Step 6: NaH (34 mg, 1.41 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (200 mg, 0.85 mmol) were added to a mixture of **36-6** (120 mg, 0.28 mmol) in DMF (10 mL). The mixture was stirred at room temperature for 1 hr. The reaction was quenched with water (10 m L) and extracted with EA (20 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 1/1) to give **Example #186** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.19 – 7.07 (m, 3H), 4.95 – 4.85 (m, 1H), 4.04 – 3.93 (m, 2H), 3.30 (t, *J* = 11.6 Hz, 2H), 2.64 – 2.57 (m, 2H), 2.43 – 2.31 (m, 2H), 1.11 – 0.97 (m, 15H). LC-MS: m/z = 496.1 $[M+H]^+$.

[00683] PREPARATIVE EXAMPLE #187, 188 and 189

[00684] Scheme 37.



[00685] Step 1: NaH (0.28 g, 7.1 mmol) and 3-bromoprop-1-ene (0.78 g, 6.5 mmol) were added to a 0°C solution of **25-6** (2.6 g, 5.9 mmol) in dry DMF (50 mL). The resulting mixture was stirred at 0°C for 3 hrs. Water was added and the solution extracted with EA (30 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluent: PE/EA = 5/1) to give **37-1** as a yellow oil. LC-MS: m/z = 481.9 $[M+H]^+$.

[00686] Step 2: m-CPBA (2.1 g, 10.4 mmol) was added at r.t.to a solution of **37-1** (2.5 g, 5.2 mmol) in 1,2-dichloroethane (40 mL). The reaction was refluxed overnight, then diluted with DCM (30 mL), washed with saturated $Na_2S_2O_3$ (50 mL), 4N NaOH (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography eluting with PE/EA = 2/1 to give **37-2** as a colorless oil. LC-MS: m/z = 497.9 $[M+H]^+$.

[00687] Step 3: NaH (60%w/w 0.08 g, 2 mmol) was added in portions to a solution of compound **37-2** (0.5 g, 1 mmol) in THF (10 mL). The mixture was stirred at room temperature overnight and then water (10 mL) was added. The mixture was extracted with EtOAc (20 mL x 2). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep. TLC to give the racemic **37-3** as

a yellow oil. LC-MS: m/z = 497.9 $[M+H]^+$.

[00688] The two isomers were seperated by chiral HPLC (IC 250 x 20 mm column. Mobile phase hexanes:ethanol 80:20 (0.1% TFA). Flow rate 20 mL/min.) with **Example #187** eluting first and **Example #188** eluting second.

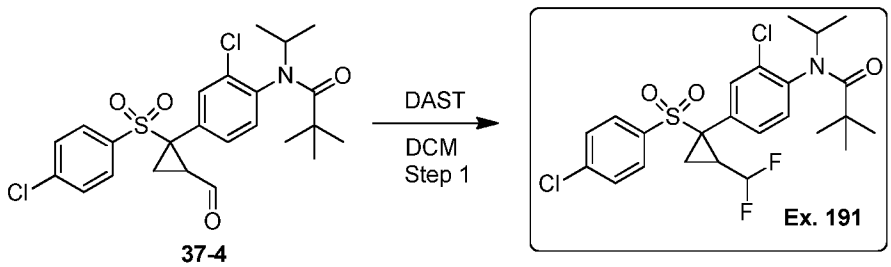
[00689] **Step 4:** PCC (0.15 g, 0.72 mmol) was added in portions.to a solution of **37-3** (0.12 g, 0.24 mmol) in DCM (10 mL). The mixture was stirred at room temperature overnight. Water (15 mL) was added and the mixture extracted with DCM (10 mL x 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep. TLC to give **37-4** as a yellow oil. LC-MS: m/z = 495.9 $[M+H]^+$.

[00690] **Step 5:** MeMgBr (3M in THF, 0.2 mL, 0.6 mmol) was added to a -45°C solution of **37-4** (0.2 g, 0.4 mmol) in THF (5 mL). The mixture was stirred at room temperature overnight and concentrated. The residue was purified by prep. TLC to give **Example 189** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.06 (m, 7H), 4.56 (s, 1H), 2.94 – 2.91 (m, 1H), 2.43 – 2.38 (m, 1H), 2.05 2.02 (m, 1H), 1.16 (m, 19H). LC-MS: 512.1 [M+1].

[00691] **Example # 190:** NaH (60%w/w 12 mg, 0.3 mmol) was added in portions to a solution of compound **37-5** (75 mg, 0.15 mmol) in THF (5 mL) followed by iodomethane (43 mg, 0.3 mmol). The mixture was stirred at room temperature overnight and concentrated. The residue was purified by prep. TLC to give **Example #190** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.16 (m, 7H), 4.61 (s, 1H), 3.08 (s, 3H), 2.42 - 2.31 (m, 2H), 2.06 - 2.01 (m, 1H), 1.73 - 1.68 (m, 1H), 1.12 - 1.07 (m, 18H). LC-MS: m/z = 525.9 $[M+H]^+$.

[00692] **PREPARATIVE EXAMPLE #191**

[00693] **Scheme 37B.**

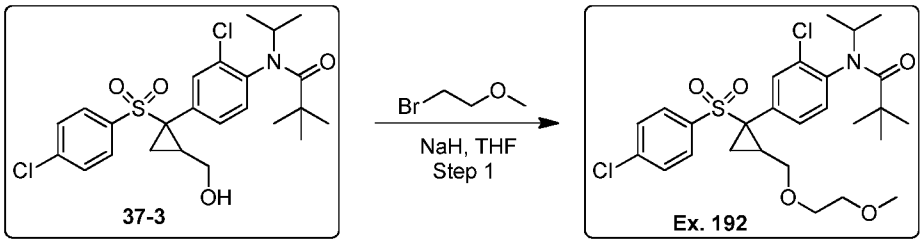


[00694] **Step 1:** DAST (97 mg, 0.6 mmol) was added to a solution of **37-4** (100 mg, 0.2 mmol) in DCM (10 mL). The mixture was stirred at room temperature overnight and then quenched with H_2O (15 mL). The mixture was extracted with DCM (10 mL X 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and

concentrated. The resulting residue was purified by prep. TLC to give **Example #191** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 7H), 5.47 - 5.41 (m, 1H), 4.53 (s, 1H), 2.81 (s, 1H), 2.20 (s, 1H), 1.85 (s, 1H), 1.11 - 1.00 (m, 15H). LC-MS: m/z = 517.9 $[M+H]^+$.

[00695] PREPARATIVE EXAMPLE #192

[00696] Scheme 37C.

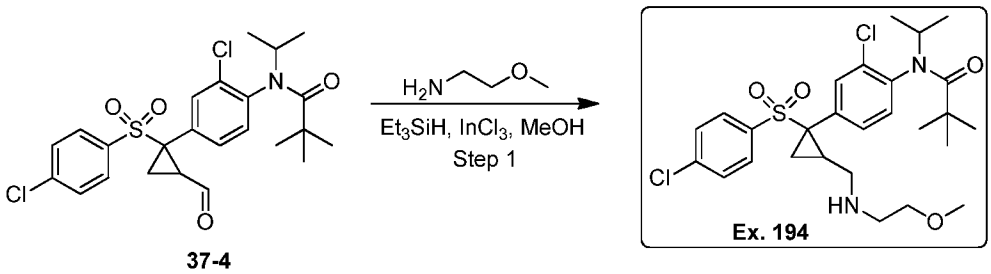


[00697] Step 1: A mixture of **37-3** (80 mg, 0.16 mmol), NaH (19 mg, 0.48 mmol) and 1-bromo-2-methoxyethane (44 mg, 0.32 mmol) was stirred at 50°C overnight. The reaction was quenched with water and extracted with EA (15 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by prep. TLC (eluent: PE/EA = 2/1) to **Example #192** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.03 (m, 7H), 4.56 (s, 1H), 3.41 - 3.30 (m, 8H), 2.95 - 2.91 (m, 1H), 2.65 (t, *J* = 15.0 Hz, 1H), 2.05 - 2.02 (m, 1H), 1.09 - 0.94 (m, 16H). LC-MS: m/z = 556.1 $[M+H]^+$.

[00698] Example #193: was prepared as described in **Scheme 38**, using 2-bromo-*N,N*-dimethylethaneamine in **step 1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.02 (m, 7H), 4.63 (s, 1H), 3.64 - 2.02 (m, 15H), 1.40 - 1.09 (m, 15H). LC-MS: m/z = 569.1 $[M+H]^+$.

[00699] PREPARATIVE EXAMPLE #194

[00700] Scheme 37D.

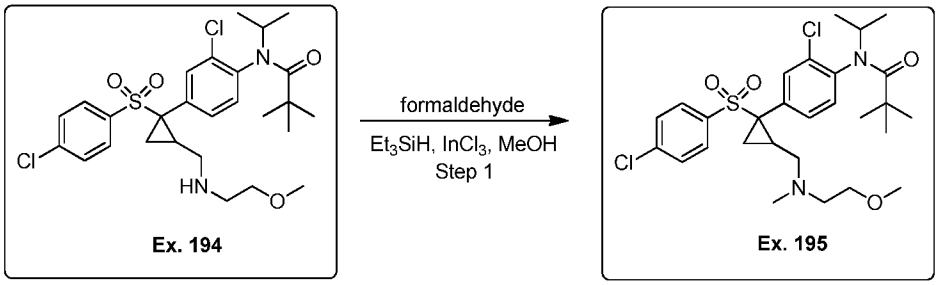


[00701] Step 1: A mixture of **37-4** (100 mg, 0.2 mmol), Et_3SiH (58 mg, 0.5 mmol), $InCl_3$ (22 mg, 0.1 mmol) and 2-methoxyethanamine (23 mg, 0.3 mmol) in MeOH (10 mL) was adjusted to pH = 6 with hydrogen chloride in EtOH. The mixture was stirred at room

temperature overnight. The mixture was evaporated and the residue purified by prep. TLC (eluent: PE/EA = 2/1) to give **Example #194** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.06 (m, 7H), 4.57 (s, 1H), 3.49 - 3.46 (m, 2H), 3.30 (s, 13H), 2.78 - 2.74 (m, 4H), 2.10 - 2.05 (m, 2H), 1.01 - 0.94 (m, 16H). LC-MS: m/z = 555.1 $[M+H]^+$.

[00702] PREPARATIVE EXAMPLE #195

[00703] Scheme 37E.



[00704] Step 1: A reaction mixture of **Example #194** (120 mg, 0.21 mmol), Et_3SiH (73 mg, 0.63 mmol), $InCl_3$ (24 mg, 0.11 mmol) and formaldehyde (63 mg, 2.1 mmol) in MeOH (10 mL) was stirred at room temperature overnight. The mixture was evaporated and the residue purified by prep. TLC (eluent: PE/EA = 2/1) to give **Example #195** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.07 (m, 7H), 4.58 (s, 1H), 3.37 - 3.28 (m, 5H), 2.26 - 1.93 (m, 10H), 1.10 - 0.95 (m, 15H). LC-MS: m/z = 568.9 $[M+H]^+$.

[00705] Example #209: was prepared as described in **Scheme 33**, using 2-morpholinoethaneamine in **step 1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.15 (br, 1H), 7.47-7.36 (m, 5H), 7.19 (d, J = 11.2 Hz, 1H),7.04 (d, J = 7.6 Hz, 1H), 4.28 (t, J = 12.0 Hz, 2H), 4.10 (s, 2H), 3.99 (s, 4H), 3.96 (br, 2H), 3.37 (d, J = 11.6 Hz, 2H), 3.20 (s, 2H), 3.00 (d, J = 11.2 Hz, 2H), 2.64 (t, J = 11.2Hz, 2H), 2.35 (d, J = 5.6 Hz, 2H), 1.07 (s, 9H). LC-MS: m/z = 567 $[M+H]^+$.

[00706] Example #210: was prepared as described in **Scheme 33**, using 2-cyclopropylethaneamine in **step 1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.18 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 11.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.02 (d, J = 10.4 Hz, 2H), 3.68-3.57 (m, 2H), 3.33 (t, J = 11.6 Hz, 2H), 2.68-2.61 (m, 2H), 2.36 (d, J = 13.6 Hz, 2H), 1.45 (q, J = 7.2 Hz, 2H) 1.09 (s, 9H), 0.60-0.58 (m, 1H), 0.46-0.43 (m, 2H), 0.08-0.04 (m, 2H). LC-MS: m/z = 522 $[M+H]^+$.

[00707] Example #211: was prepared as described in **Scheme 33**, using (S)-1-cyclohexylethaneamine in **step 1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (s, 4H), 7.14 (t, J =

8.0 Hz, 1H), 7.07 (d, J = 11.6 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.62 (br, 1H), 4.03 (d, J = 11.2 Hz, 2H), 3.30 (t, J = 11.2 Hz, 2H), 2.67 (t, J = 10.4 Hz, 2H), 2.37 (d, J = 10.4 Hz, 2H), 1.99 (m, 1H), 1.77-1.67 (m, 4H), 1.25-0.82 (m, 18H). LC-MS: m/z = 564 $[M+H]^+$.

[00708] Example #212: was prepared as described in **Scheme 33**, using (R)-3,3-dimethylbutan-2-amine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.33 (m, 5H), 7.04 (d, J = 10.8 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 5.13 (br, 1H), 4.02 (d, J = 10.8Hz, 2H), 3.30 (q, J = 11.2 Hz, 2H), 2.70 (t, J = 10.4 Hz, 2H), 2.36 (d, J = 12.8 Hz, 2H), 1.01-0.87 (m, 21H). LC-MS: m/z = 538 $[M+H]^+$.

[00709] Example #213: was prepared as described in **Scheme 33**, using (S)-3,3-dimethylbutan-2-amine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.33 (m, 5H), 7.04 (d, J = 10.8 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 5.13 (br, 1H), 4.02 (d, J = 10.8Hz, 2H), 3.30 (q, J = 11.2 Hz, 2H), 2.70 (t, J = 10.4 Hz, 2H), 2.36 (d, J = 12.8 Hz, 2H), 1.01-0.87 (m, 21H). LC-MS: m/z = 538 $[M+H]^+$.

[00710] Example #214: was prepared as described in **Scheme 33**, using 2-cyclohexylethaneamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.32 (m, 4H), 7.17 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 11.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.00 (d, J = 10.4 Hz, 2H), 3.59 (br, 1H), 3.31 (t, J = 10.4 Hz, 2H), 2.65 (t, J = 13.6 Hz, 2H), 2.35 (d, J = 13.6 Hz, 2H), 1.70-1.57 (m, 6H), 1.42-1.37 (m, 2H), 1.24-1.14 (m, 4H), 1.08 (s, 9H), 0.96-0.86 (m, 2H). LC-MS: m/z = 564 $[M+H]^+$.

[00711] Example #215: was prepared as described in **Scheme 33**, using (1-methyl-1H-pyrazol-4-yl)methaneamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (m, 5H), 7.15-7.02 (m, 2H), 6.92-6.87 (m, 2H), 3.99 (d, J = 12.0 Hz, 2H), 3.85 (s, 3H), 3.26 (t, J = 11.6Hz, 2H), 2.66-2.59 (m, 2H), 2.31 (d, J = 13.2 Hz, 2H), 1.07 (s, 9H). LC-MS: m/z = 548 $[M+H]^+$.

[00712] Example #216: was prepared as described in **Scheme 33**, using (S)-1-cyclopropylethanamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (m, 5H), 7.07-6.99 (m, 2H), 4.10 (br, 1H), 4.01 (d, J = 12.0 Hz, 2H), 3.24-3.30 (m, 2H), 2.71-2.64 (m, 2H), 2.36 (d, J = 14.0 Hz, 2H), 1.14-1.13 (m, 3H), 1.05 (s, 9H), 0.42-0.39 (m, 5H). LC-MS: m/z = 522 $[M+H]^+$.

[00713] Example #217: was prepared as described in **Scheme 33**, using (R)-1-cyclopropylethanamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (m, 5H), 7.07-6.99 (m, 2H), 4.10 (br, 1H), 4.01 (d, J = 12.0 Hz, 2H), 3.24-3.30 (m, 2H), 2.71-2.64 (m, 2H), 2.36 (d, J = 14.0 Hz, 2H), 1.14-1.13 (m, 3H), 1.05 (s, 9H), 0.42-0.39 (m, 5H). LC-MS: m/z =

522 $[M+H]^+$.

[00714] Example #218: was prepared as described in **Scheme 33**, using (4-fluorophenyl)methanamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (m, 4H), 7.14-7.07 (m, 2H), 6.92-6.87 (m, 2H), 6.82-6.80 (m, 2H), 3.99 (d, J = 10.0 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 2.66-2.59 (m, 2H), 2.28 (d, J = 13.2 Hz, 2H), 1.07 (s, 9H). LC-MS: m/z = 562 $[M+H]^+$.

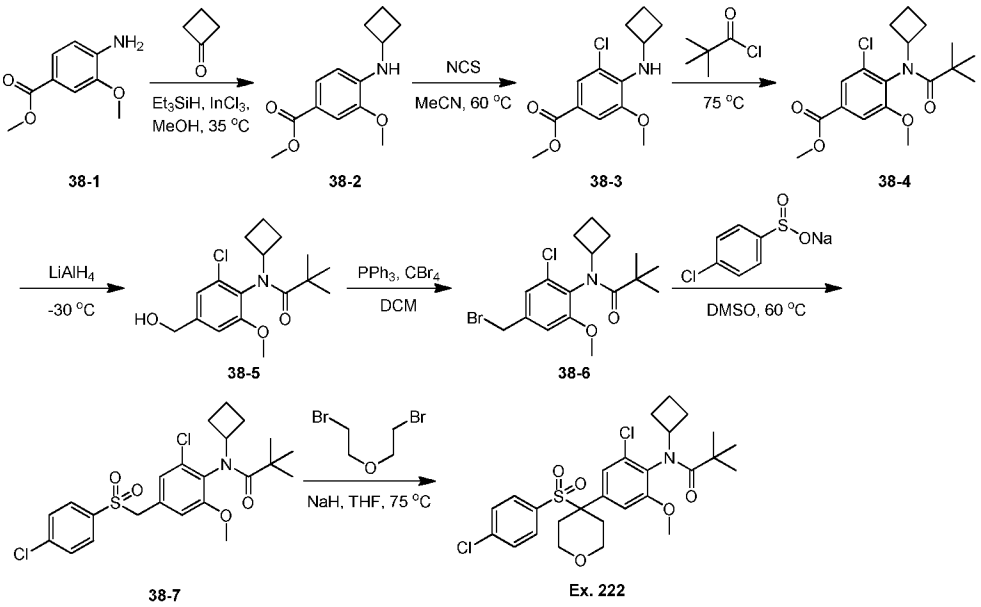
[00715] Example #219: was prepared as described in **Scheme 33**, using (R)-1-cyclopropylpropan-2-amine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.34 (m, 4H), 7.16 (t, J = 8.0 Hz, 1H), 7.07-7.01 (m, 2H), 4.68 (br, 1H), 4.05 (d, J = 10.0Hz, 2H), 3.46 (t, J = 11.6 Hz, 2H), 2.73 (t, J = 3.2 Hz, 2H), 2.38 (d, J = 13.6 Hz 2H), 1.57-1.53 (m, 1H) 1.11-1.07 (m, 13H), 0.70-0.68 (m, 1H), 0.52-0.48 (m, 2H), 0.18-0.97 (m, 2H). LC-MS: m/z = 536 $[M+H]^+$.

[00716] Example #220: was prepared as described in **Scheme 33**, using (S)-1-cyclopropylpropan-2-amine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.34 (m, 4H), 7.16 (t, J = 8.0 Hz, 1H), 7.07-7.01 (m, 2H), 4.68 (br, 1H), 4.05 (d, J = 10.0Hz, 2H), 3.46 (t, J = 11.6 Hz, 2H), 2.73 (t, J = 3.2 Hz, 2H), 2.38 (d, J = 13.6 Hz 2H), 1.57-1.53 (m, 1H) 1.11-1.07 (m, 13H), 0.70-0.68 (m, 1H), 0.52-0.48 (m, 2H), 0.18-0.97 (m, 2H). LC-MS: m/z = 536 $[M+H]^+$.

[00717] Example #221: was prepared as described in **Scheme 33**, using (R)-1-cyclobutylethanamine in **step 1**. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37 (s, 4H), 7.07-7.00 (m, 3H), 4.01 (d, J = 12.0 Hz, 2H), 3.34 (t, J = 11.6 Hz, 2H), 2.73-2.66 (m, 2H), 2.39 (d, J = 14.0 Hz, 2H), 1.07 (s, 9H), 0.89 (s, 3H). LC-MS: m/z = 536 $[M+H]^+$.

[00718] PREPARATIVE EXAMPLE #222:

[00719] SCHEME 38.



[00720] Step 1: To a solution compound **38-1** (8.0 g, 44 mmol, 1.0 eq.) in dry MeOH (80 mL) were added cyclobutanone (6.2 g, 88 mmol, 2.0 eq.) and $InCl_3$ (4.9 g, 22 mmol, 0.5 eq.), and then the mixture was stirred at 35 °C for 2.5 h. TLC (PE/EA = 6/1) showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. The residue was partitioned between EA (100 mL) and water (150 mL) and the aqueous layer was extracted with EA (100 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography, eluted with PE/EA (50/1 ~ 30/1) to give compound **38-2** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.62 (dd, J = 8.4, 1.6 Hz,1H), 7.40 (d, J = 1.6 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 4.83 (br, 1H), 3.98-3.95 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.48-2.45 (m, 2H), 1.91-1.82 (m, 4H).

[00721] Step 2: A mixture of compound **38-2** (4.0 g, 17 mmol, 1.0 eq.) and NCS (3.0 g, 22.1 mmol, 1.3 eq.) in MeCN (50 mL) was stirred at 60 °C for 3 h. TLC (PE/EA = 8/1) showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. To the residue was added EA (100 mL), NaOH aq (22 mL, 1 mol/L) and water (150 mL) with stirring. The aqueous layer was separated and extracted with EA (100 mL x 3). The combined organic layers were washed with water (150 mL) and brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column

chromatography, eluted with PE/EA (40/1 ~ 20/1) to give compound **38-3** as an oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.6 (d, *J* = 1.6 Hz,1H), 7.35 (d, *J* = 1.6 Hz, 1H), 4.58 (br, 1H), 4.47-4.43 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.37-2.32 (m, 2H), 1.89-1.83 (m, 2H), 1.74-1.63 (2H).

[00722] Step 3: A mixture of compound **38-3** (2.2 g, 8.1 mmol, 1.0 eq.) in pivaloyl chloride (20 mL) was stirred at 75 °C for 1.5 h. LCMS showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. The residue was purified by column chromatography, eluted with PE/EA (40/1 ~ 20/1) to give compound **38-4** as a colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.50 (s, 1H), 4.66-4.62 (m, 1H) 3.95 (s, 3H), 3.90 (s, 3H), 2.10-2.08 (m, 2H), 1.73-1.54 (m, 4H), 0.98 (s, 9H).

[00723] Step 4: To a solution of compound **38-4** (2.3 g, 6.5 mmol, 1.0 eq.) in dry THF (50 mL) was added in portions LAH (0.62 g, 16.3 mmol, 2.5 eq.) at -30 °C, and then the mixture was stirred at -30 °C for 20 min. TLC (PE/EA = 3/1) showed that the reaction was complete. To the mixture was added dropwise water (0.6 mL) at -40 ~ -20 °C followed by 15% aq. NaOH (0.6 mL) and water (1.5 mL). Na_2SO_4 (ca. 10 g) was added and the mixture was stirred at room temperature for 15 min. The mixture was filtered, and the filter cake was washed with EA (20 mL x 3). The combined filtrates were concentrated in vacuum. The residue was purified by re-crystallization from PE/EA (30 mL/3 mL) to give compound **38-5** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 6.91 (s, 1H), 4.73-4.72 (d, *J* = 4.8 Hz, 2H), 4.68-4.62 (m, 1H), 3.83 (s, 3H), 2.11-2.06 (m, 3H), 1.75-1.72 (m, 2H), 1.58-1.53 (m, 2H), 0.98 (s, 9H).

[00724] Step 5: To a solution of compound **38-5** (1.0 g, 3.1 mmol, 1.0 eq) in dry DCM (20 mL) were added PPh_3 (1.2 g, 4.7 mmol, 1.5 eq) and CBr_4 (1.56 g, 4.7 mmol, 1.5 eq) at 0~5 °C under nitrogen, and then the mixture was stirred at room temperature for 1 h. TLC (PE/EA = 3/1) showed that most of compound **38-5** was consumed. The mixture was concentrated in vacuum and the residue was purified by column chromatography, eluted with PE/EA (12/1 ~ 10/1) to give compound **38-6** as a white solid. ^{1}HNMR: (400 MHz, DMSO) δ: 7.30 (s, 1H), 7.25 (s, 1H), 4.72 (s, 2H), 4.56-4.52 (m, 1H), 3.83 (s, 3H), 1.99-1.96 (m, 2H), 1.67-1.52 (m, 4H), 0.89 (s, 9H).

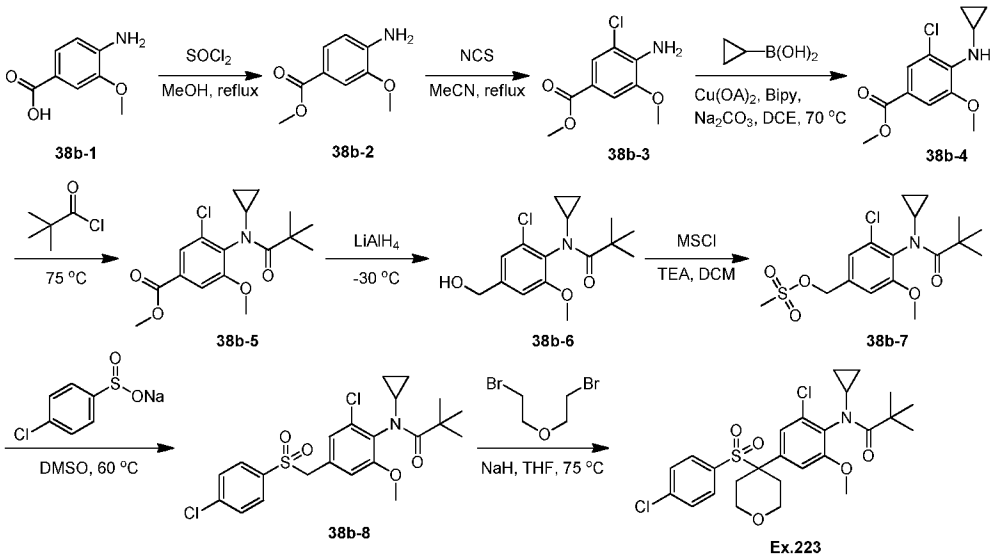
[00725] Step 6: To a solution of sodium 4-chlorobenzenesulfinate (230 mg, 1.16 mmol, 1.05 eq) in DMSO (6 mL) was added compound **38-6** (428 mg, 1.1 mmol, 1.0 eq) in portions at 60 °C, and then the mixture was stirred at 60 °C for 1 h. TLC (PE/EA = 3/1) showed that the reaction was complete. The mixture was cooled to room temperature, and poured into water

(50 mL) with stirring. The formed solid was collected by filtration, washed with water (10 mL x 2), then dissolved in EA (30 mL). The obtained organic solution was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by re-crystallization from PE/EA (12 mL/3 mL) to give compound **38-7** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 8.8 Hz, 2H), 7.4 (d, *J* = 8.8 Hz, 2H), 6.69 (s, 1H), 6.61 (s, 1H), 4.62-4.60 (m, 1H), 4.29 (s, 2H), 3.73 (s, 3H), 2.08-2.06 (m, 2H), 1.61-1.40 (m, 4H), 0.96 (s, 9H).

[00726] Step 7: To a solution of **38-7** (242 mg, 0.5 mmol, 1.0 eq) in THF (6 mL) were added NaH (120 mg, 3 mmol, 6.0 eq, 60% dispensed in mineral oil) and bis(2-bromoethyl) ether (255 mg, 1.1 mmol, 2.2 eq), and then the mixture was stirred at 75 °C for 6 h. LCMS showed that the reaction was complete. The mixture was cooled to room temperature, and poured into water (30 mL). The mixture was extracted with EA (20 mL x2) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: Synergi 150*30mm; Detection wavelength: 220nm) to give **Example #222** as a white solid. ^{1}HNMR: (400 MHz, DMSO) δ: 7.55 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 4.65-4.55 (m, 1H), 3.96-3.92 (m, 2H), 3.68 (s, 3H), 3.22 (t, *J* = 11.2 Hz, 2H), 2.52-2.43 (m, 4H), 2.12-2.01 (m, 2H), 1.70-1.56 (m, 4H), 0.99 (s, 9H). LCMS(ESI): (M+Na: 576).

[00727] PREPARATIVE EXAMPLE #223:

[00728] SCHEME 38b.



[00729] Step1: To a mixture of compound **38b-1** (25.5 g, 153 mmol, 1.0 eq.) in dry MeOH (250 mL) was added dropwise $SOCl_2$ (50 mL) under ice-water bath, and then the mixture was stirred at reflux overnight. TLC (PE/EA = 2/1) showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. The mixture was diluted with water (500 mL), basified to pH = 9 with 1 N aq. NaOH, and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated to give target compound **38b-2**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.40 (dd, *J* = 8.4, 1.6 Hz,1H), 7.29 (d, *J* = 1.6 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.65 (br, 2H), 3.81 (s, 3H), 3.76 (s, 3H).

[00730] Step 2: A mixture of compound **38b-2** (12.0 g, 66 mmol, 1.0 eq.) in MeCN (150 mL) and NCS (13 g, 99 mmol, 1.5 eq.) was stirred at 90 °C for 5 h. TLC (PE/EA = 3/1) showed that most of compound **38b-2** was converted into target compound. Then the mixture was concentrated under reduced pressure. The residue was dissolved in saturated aqueous K_2CO_3 solution (500 mL) and EA (200 mL). The aqueous layer was extracted with EA (300 mL x 3). The combined organic layer were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (25/1 ~ 15/1) to give compound **38b-3**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.48 (s, 1H), 7.27 (s, 1H), 5.81 (br, 2H), 3.86 (s, 3H), 3.79 (s, 3H).

[00731] Step 3: A mixture of compound 38b-3 (5.0 g, 23 mmole, 1.0 eq.), cyclopropylboronic acid (4.0 g, 46 mmol, 2.0 eq.), Cu(OAc)2 (5.1 g, 28 mmol, 1.2 eq.), Bipy (4.4 g, 28 mmol, 1.2 eq.) and Na2CO3 (4.9 g, 46 mmol, 2.0 eq.) in DCE (60 mL) was stirred at 70 oC for 3.5 h. The mixture was then cooled to room temperature and filtered, and the filter cake was washed with DCM (20 mL x 3). The combined filtrates were concentrated in vacuum and the residue was purified by column chromatography, eluted with PE/EA (30/1) to give 38b-4. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.64 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H), 4.68 (br, 1H), 3.87 (s, 6H), 3.10-3.07 (m, 1H), 0.76-0.69 (m, 2H), 0.58-0.51 (m, 2H).

[00732] Step 4: A mixture of **38b-4** (2.0 g, 7.8 mmol, 1.0 eq.) in pivaloyl chloride (20 mL) was stirred at 75 °C for 2 h. TLC (PE/EA = 2/1) showed that the reaction was complete. The mixture was slowly poured into water (150 mL) and then basified to12~13 by slow addition of solid NaOH. The mixture was extracted with EA (60 mL x 3) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography, eluted with PE/EA (20/1 ~ 15/1) to give compound **38b-5**. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 7.46 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.15-3.13 (m, 1H), 0.98 (s, 9H), 0.65-0.63 (m, 2H), 0.57-0.4 (m, 2H). LCMS(ESI): (M+1: 339.9).

[00733] Step 5 To a solution of **38b-5** (1.6 g, 4.7 mmol, 1.0 eq.) in anhydrous THF (20 mL) was added in portions LAH (0.39 g, 10.3 mmol, 2.2 eq.) at -30 °C, and then the mixture was stirred at -30 °C for 20 min. TLC (PE/EA = 1/1) showed that the reaction was complete. To the mixture was added dropwise water (0.4 mL) at -30 °C followed by 15% aq. NaOH (0.4 mL) and water (1 mL). Anhydrous Na_2SO_4 (ca. 10 g) was added and the mixture was slowly warmed to 0 °C. After stirring for 30 min, the mixture was filtered and the filter cake was washed with EA (10 mL x 2). The combined filtrates were concentrated in vacuum to give compound **38b-6** which was directly used in the next step without further purification. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.04 (s, 1H), 6.87 (s, 1H), 4.71 (s, 2H), 3.81 (s, 3H), 3.15-3.12 (m, 1H), 2.30 (br, 1H), 0.99 (s, 9H), 0.63-0.41 (m, 4H). LCMS(ESI): (M+1: 311.8).

[00734] Step 6: To a solution of **38b-6** (400 mg, 1.6 mmol, 1.0 eq.) in dry DCM (12 mL) was added dropwise TEA (323 mg, 3.2 mmol, 2.0 eq.) and MsCl (274 mg, 2.4 mmol, 1.5 eq.) under ice-water bath, and then the mixture was stirred at room temperature for 15 min. LCMS showed that the reaction was complete. The mixture was diluted with DCM (20 mL), washed with water (40 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated to give crude compound **38b-7** which was directly used in the next step without further

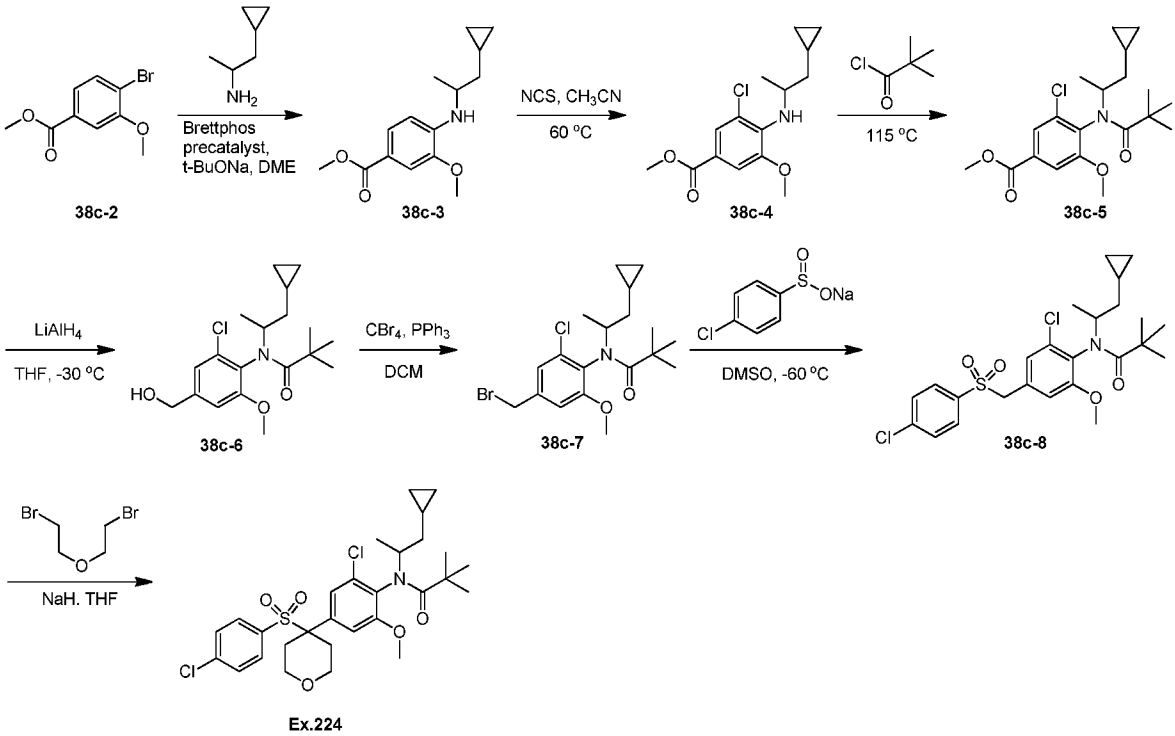
purification. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.10 (s, 1H), 6.86 (s, 1H), 5.17 (s, 2H), 3.84 (s, 3H), 3.36-3.12 (m, 1H), 3.06 (s, 3H), 0.99 (s, 9H), 0.65-0.41 (m, 4H).

[00735] Step 7: To a solution of sodium 4-chlorobenzenesulfinate (400 mg, 2.0 mmol, 1.2 eq.) in DMSO (5 mL) was added a solution of **38b-7** (660 mg, 1.7 mmol, 1.0 eq.) in DMSO (10 mL) dropwise at 60 °C, and then the mixture was stirred at 60 °C for 2 h. TLC (PE/EA = 2/1) showed that the reaction was complete. The mixture was cooled to room temperature, and poured into water (80 mL) under stirring. The solid was collected by filtration, washed with water (10 mL x 2), and then dissolved in EA (80 mL). The obtained organic solution washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by re-crystallization from PE/EA (10 mL/3 mL) to give product **38b-8**. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.69 (s, 1H), 6.60 (s, 1H), 4.28 (s, 2H), 3.81 (s, 3H), 3.12-3.10 (m, 1H), 0.98 (s, 9H), 0.64-0.35 (m, 4H).

[00736] Step 8: To a solution of **38b-8** (300 mg, 0.64 mmol, 1.0 eq.) in THF (8 mL) were added NaH (152 mg, 3.8 mmol, 6.0 eq., 60% in mineral oil) and bis(2-bromoethyl) ether (327 mg, 1.4 mmol, 2.2 eq.), and then the mixture was stirred at 75 °C overnight. LCMS showed that the reaction was complete. The mixture was cooled to room temperature, and slowly poured into water (20 mL). The aqueous mixture was extracted with EA (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: YMC 150*30mm; Detection wavelength: 220nm) to give **Example # 223**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.57(d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 1.6 Hz 1H), 6.76 (d, *J* = 1.6 Hz, 1H), 3.94 (d, *J* = 11.6 Hz, 2H), 3.64 (s, 3H), 3.21-3.10 (m, 3H), 2.55-2.50 (m, 2H), 2.43-2.35 (m, 2H), 1.05 (s, 9H), 0.69-0.35 (m, 4H). LCMS(ESI): (M+Na: 562).

[00737] PREPARATIVE EXAMPLE #224:

[00738] SCHEME 38c.



[00739] Step1: To a solution of compound **38c-2** (3.5 g, 14.3 mmol, 1.0 eq.) in DME (30 mL) were added 1-cyclopropylpropan-2-amine (1.7 g, 17.2 mmol, 1.2 eq.), *t*-BuONa (3.0 g, 31.5 mmol, 2.2 eq.) and pre-Pd-brettphos (0.46 g, 0.572 mmol, 0.04 eq.) under N_2, and then the mixture was stirred at 95 °C under N_2 overnight. TLC (PE/EA = 15/1) showed that the reaction was complete. The reaction mixture was concentrated in vacuum. The residue was portioned between EA (150 mL) and water (300 mL). The aqueous layer was separated and extracted with EA (150 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted by PE/EA (50/1 ~ 35/1) to give compound **38c-3** as an oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.65 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.42 (d, *J* = 1.2 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.69 (br, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.70-3.51 (m, 1H), 1.62-1.56 (m, 1H), 1.42-1.38 (m, 1H), 1.49 (d, *J* = 6.0 Hz, 3H), 0.77-0.75 (m, 1H), 0.52-0.49 (m, 2H), 0.13-0.09 (m, 2H).

[00740] Step 2: To a solution of compound **38c-3** (1.05 g, 4.0 mmol, 1.0 eq.) in MeCN (16 mL) was added NCS (0.56 g, 4.2 mmol, 1.05 eq.) at 70 °C for 3 h. TLC (PE/EA = 5/1) showed that the reaction was complete. The reaction mixture was concentrated and the residue was purified by column chromatography, eluted by PE/EA (60/1 ~ 50/1) to give

compound **38c-4**. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.68 (s, 1H), 7.39 (s, 1H), 4.41 (br, 1H), 4.30-4.26 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 1.52-1.48 (m, 1H), 1.32-1.27 (m, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.73-0.71 (m, 1H), 0.48-0.45 (m, 2H), 0.07-0.06 (m, 2H).

[00741] Step 3: A mixture of compound **38c-4** (1.0 g, 3.4 mmol, 1.0 eq.) in pivaloyl chloride (12 mL) was stirred at 115 °C for 6 h. TLC (PE/EA = 8/1) showed that the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography, eluted by PE/EA (45/1 ~ 35/1) to give compound **38c-5**. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.50 (s, 0.5H), 7.49 (s, 0.5H), 4.05-4.02 (m, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 1.66-1.62 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 1.5H), 1.18 (d, *J* = 6.8 Hz, 1.5H), 0.98 (s, 9H), 0.75-0.60 (m, 1H), 0.45-0.37 (m, 2H), 0.10-0.07 (m, 2H).

[00742] Step 4: To a solution of compound **38c-5** (0.85 g, 2.2 mmol, 1.0 eq.) in anhydrous THF (30 mL) was added LAH (0.21 g, 5.5 mmol, 2.5 eq.) in portions at -35 ~ -25 °C, and then the mixture was stirred at -30 °C for 30 min. TLC (PE/EA = 3/1) showed that the reaction was complete. The reaction was quenched by slow addition of water (0.2 mL), followed by 15% aq. NaOH (0.2 mL) and water (0.6 mL) at -35 ~ -20 °C. To the mixture was added Na_2SO_4 (ca. 25 g) and the mixture was stirred at room temperature for 20 min. The mixture was filtered, and the filter pad was washed with EA (20 mL x 3). The combined filtrates were concentrated in vacuum and the residue was purified by column chromatography, eluted by PE/EA (6/1 ~ 3/1) to give target compound **38c-6** as a colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.05 (s, 1H), 6.88 (s, 0.5H), 6.86 (s, 0.5H), 4.74 (d, *J* = 6.4 Hz, 2H), 4.12-4.07 (m, 1H), 3.85 (s, 1.5H), 3.84 (s, 1.5H), 1.94 (t, *J* = 6.4 Hz, 1H), 1.65-1.58 (m, 2H), 1.19 (d, *J* = 7.2 Hz, 1.5H), 1.17 (d, *J* = 7.2 Hz, 1.5H), 0.98 (s, 9H), 0.70-0.60 (m, 1H), 0.45-0.38 (m, 2H), 0.10-0.08 (m, 2H).

[00743] Step 5: To a solution of compound **38c-6** (0.78 g, 2.2 mmol, 1.0 eq.) in anhydrous DCM (25 mL) were added PPh_3 (0.86 g, 3.3 mmol, 1.5 eq.) and CBr_4 (1.1 g, 3.3 mmol, 1.5 eq) under ice-water bath, and then the mixture was stirred at room temperature for 1 h. TLC (PE/EA = 3/1) showed that the reaction was complete. The mixture was concentrated in vacuum and the residue was purified by column chromatography, eluted by PE/EA (50/1 ~ 40/1) to give compound **38c-7** as a colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$, rotamer) δ: 7.10 (s, 1H), 6.85 (s, 0.5H), 6.84 (s, 0.5H), 4.45 (s, 2H), 4.15-4.00 (m, 1H), 3.86 (s, 1.5H), 3.85 (s, 1.5H), 1.66-1.061 (m, 2H), 1.20 (d, *J* = 6.8 Hz, 1.5H), 1.18 (d, *J* = 6.8 Hz, 1.5H), 0.98 (s, 9H), 0.70-0.60 (m, 1H), 0.45-0.37 (m, 2H), 0.02-0.08 (m, 2H).

[00744] Step 6: To a solution of sodium 4-chlorobenzenesulfinate (0.42 g, 2.1 mmol, 1.1 eq.) in DMSO (10 mL) was added compound **38c-7** (0.8 g, 1.9 mmol, 1.0 eq.) portion wise at 60 °C, and then the mixture was stirred at 60 °C for 1 h. TLC (PE/EA = 3/1) showed that the reaction was complete. The mixture was cooled to room temperature, poured into ice-water (50 mL) under stirring. The formed solid was collected by filtration, washed with water (5 mL x 2), and then dissolved in EA (30 mL). The obtained solution was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted by PE/EA (6/1 ~ 5/1) to give compound **38c-8** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.60 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.71 (s, 0.5H), 6.69 (s, 0.5H), 6.61 (s, 0.5H), 6.58 (s, 0.5H), 4.29 (s, 2H), 4.08-4.04 (m, 1H), 3.75 (s, 1.5H), 3.73 (s, 1.5H), 1.58-1.52 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 1.5H), 1.10 (d, *J* = 7.2 Hz, 1.5H), 0.96 (s, 9H), 0.70-0.60 (m, 1H), 0.46-0.39 (m, 2H), 0.09-0.07 (m, 2H).

[00745] Step 7: To a solution of compound **38c-8** (300 mg, 0.59 mmol, 1.0 eq.) in anhydrous THF (8 mL) were added NaH (142 mg, 3.54 mmol, 6.0 eq., 60% dispensed in mineral oil) and bis(2-bromoethyl) ether (302 mg, 1.3 mmol, 2.2 eq), and then the mixture was stirred at 85 °C for 4.5 h. TLC (PE/EA = 3/1) showed that the reaction was complete. The mixture was cooled to room temperature, poured into ice-water (50 mL) under stirring, and then extracted with EA (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: Synergi 150 x 30 mm; Detection wavelength: 220 nm) to afford **Example # 224** as a white solid. ^{1}HNMR: (400 MHz, DMSO) δ: 7.54 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.03 (s, 0.5H), 7.02 (s, 0.5H), 6.70 (s, 0.5H), 6.67 (s, 0.5 H), 3.92-3.88 (m, 3H), 3.61 (s, 1.5H), 3.60 (s, 1.5H), 3.10-3.04 (m, 2H), 2.58-2.51 (m, 2H), 2.36-2.30 (m, 2H), 1.51-1.40 (m, 2H), 1.06 (d, *J* = 7.6 Hz, 1.5H), 1.03 (d, *J* = 7.6 Hz, 1.5H), 0.87 (s, 9H), 0.70-0.60 (m, 1H), 0.46-0.39 (m, 2H), 0.06-0.02 (m , 2H). LCMS(ESI): (M+Na: 604).

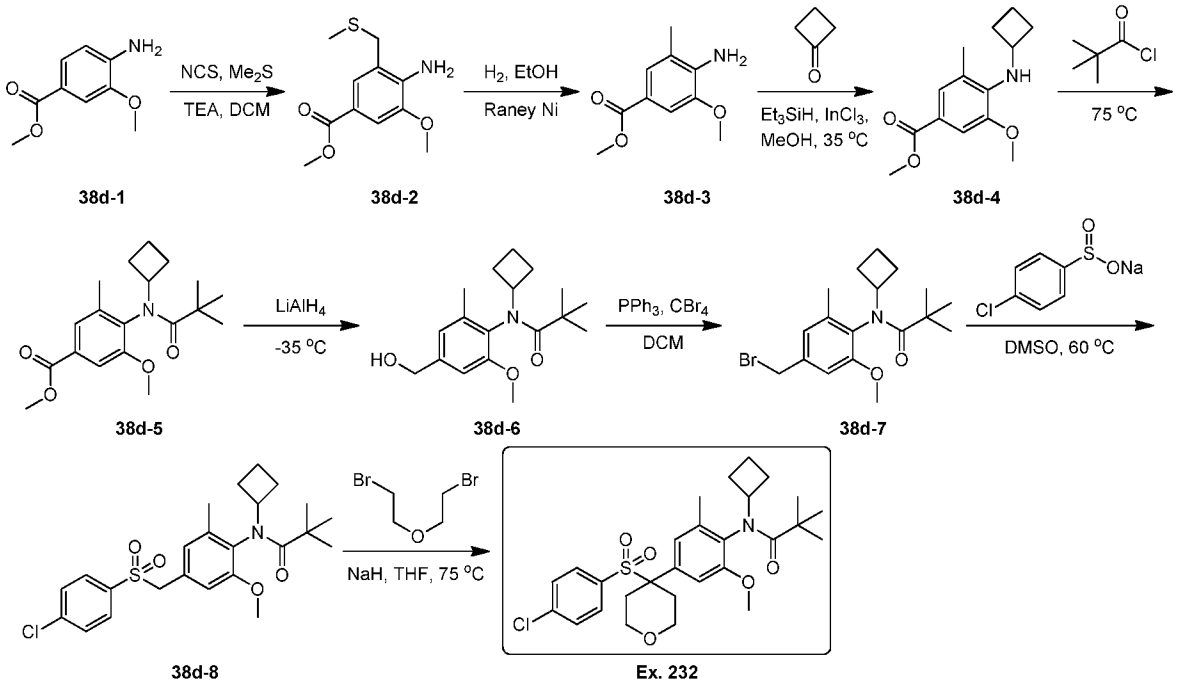
[00746] Example #225: was prepared as described in **Scheme 38c**, using (R) cyclohexylethanamine in **step 1**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.56 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.04 (s, 0.5H), 7.02 (s, 0.5H), 6.69 (s, 0.5H), 6.65 (s, 0.5H), 3.91 (d, J = 10.0 Hz, 2H), 3.82-3.79 (m, 1H), 3.61 (s, 1.5H), 3.59 (s, 1.5H), 3.11-3.05 (m, 2H), 2.60-2.51 (m, 2H), 2.36-2.30 (m, 2H), 1.85-1.60 (m, 6H), 1.10-0.88 (m, 17H). LCMS(ESI): (M+Na: 632).

[00747] Example #226: was prepared as described in **Scheme 38c**, using (S)-1-

cyclohexylethanamine and cyclopropanecarbonyl chloride in **step 3**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.54 (d, J = 8.4 Hz, 2H), 7.44-7.37 (m, 4H), 4.40-4.36 (m, 0.6H), 4.18-4.13 (m, 0.4H), 3.89 (d, J = 11.6 Hz, 2H), 3.18 (t, J = 12.4 Hz, 2H), 2.52 (d, J = 1.6 Hz, 2H), 2.50-2.31 (m, 2H), 1.77-1.41 (m, 6H), 1.09-0.68 (m, 14H). LCMS(ESI): (M+Na: 616).

[00748] PREPARATIVE EXAMPLE #232:

[00749] SCHEME 38d.



[00750] Step 1: To a solution of compound **38d-1** (14.0 g, 77.0 mmol, 1.0 eq.) and Me_2S (5.7 g, 92.4 mmol, 1.2 eq) in anhydrous DCM (200 mL) was added in portions NCS (12.3 g, 92.4 mmol, 1.2 eq) at 80 °C, and then the mixture was stirred at room temperature for 40 min. To the mixture was added TEA (11.7 g, 115.5 mmol, 1.5 eq), and then the mixture was stirred at 65 °C for 3 h. TLC (PE/EA = 3/1) showed that most of compound **38d-1** was converted into **38d-2**. The mixture was washed with 10% aq. NaOH (40 mL x 2) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (9/1 ~ 7/1) to give crude **38d-2** which was purified further by re-crystallization from PE/EA (3/1, 50 mL) to give pure compound **38d-2** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.44 (s, 1H), 7.42 (s, 1H), 4.69 (br, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.72 (s, 2H), 1.97 (s, 3H).

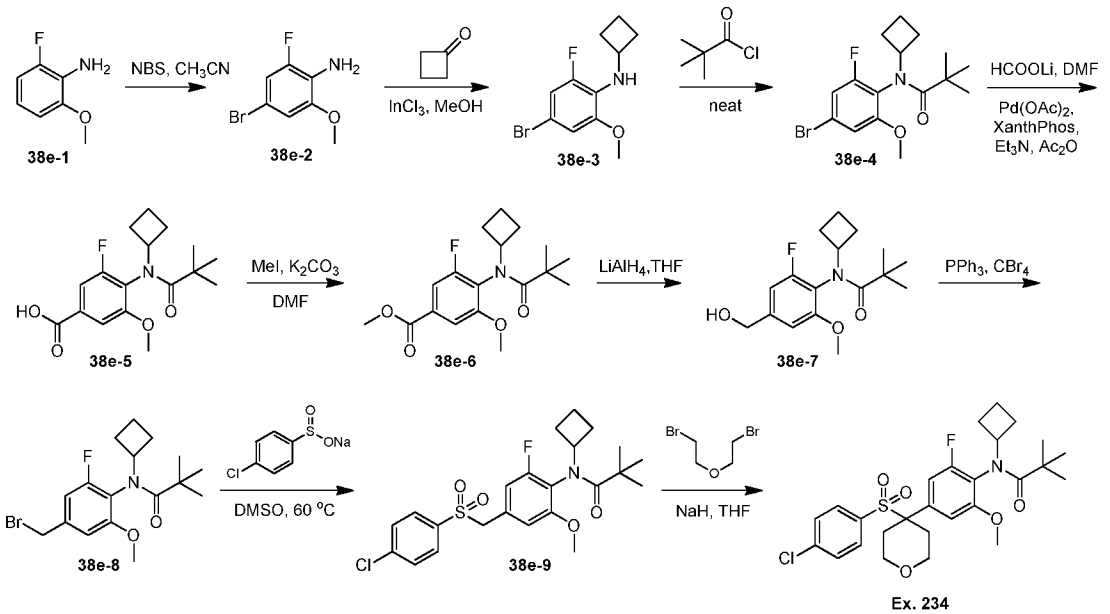
[00751] Step 2: A mixture of compound **38d-2** (6.3 g, 26 mmol, 1.0 eq.) and Raney Ni (63 g) in EtOH (150 mL) was stirred at 30 °C under 50 psi of hydrogen pressure for 2.5 h. TLC (PE/EA = 3/1) showed that the reaction was complete. The mixture was filtered, and the filter cake was washed with EtOH (100 mL x 4). The combined filtrates were concentrated to give crude compound **33d-3** as a colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.48 (s, 1H) 7.36 (s, 1H), 4.18 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 2.19 (s, 3H).

[00752] Example #232: was prepared as described in **Scheme 38**, using compound **38d-3** as starting material in **step 1**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.51 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.77 (s, 1H), 6.63 (s, 1H), 4.52-4.47 (m, 1H), 3.95-3.92 (m, 2H), 3.62 (s, 3H), 3.23-3.18 (m, 2H), 2.51-2.40 (m, 4H), 2.17-2.05 (m, 5H), 1.73-1.57 (m, 4H), 0.95 (s, 9H). LCMS(ESI): (M+Na: 556).

[00753] Example #233: was prepared as described in **Scheme 38b**, using compound **38d-3** as starting material in **step 3**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.53 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.73 (s, 1H), 6.60 (s, 1H), 3.94 (d, *J* = 11.6 Hz, 2H), 3.58 (s, 3H), 3.21-3.19 (m, 3H), 2.51-2.42 (m, 4H), 2.06 (s, 3H), 1.06 (s, 9H), 0.67-0.64 (m, 2H), 0.39-0.26 (m , 2H). LCMS(ESI): (M+Na: 542).

[00754] PREPARATIVE EXAMPLE #234:

[00755] SCHEME 38e.



[00756] Step 1: To a solution compound **38e-1** (1.41 g, 10 mmol, 1.0 eq.) in CH_3CN (50 mL) was added NBS (1.96 g, 11 mmol, 1.1 eq.) in portions at room temperature. The mixture was stirred at room temperature for 2 h, at which time TLC (PE/EA = 5/1) showed

the reaction was complete. The mixture was concentrated in vacuum. The residue was dissolved in EA (50 mL), washed with water (50 mL x 2), saturated aqueous $NaHCO_3$ (50 mL x 2) and brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum to give crude product **38e-2** as a black oil, which was directly used in the next step without further purification. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 6.95 (d, *J* = 10.0 Hz, 1H), 6.85 (s, 1H), 4.82 (br, 2H), 3.80 (s, 3H).

[00757] Step 2: To a solution compound **38e-2** (6.6 g, 30 mmol, 1.0 eq.) and Et_3SiH (8.7 g, 75 mmol, 2.5 eq.) in dry MeOH (60 mL) were added cyclobutanone (3.2 g, 45 mmol, 1.5 eq.) and $InCl_3$ (0.99 g, 4.5 mmol, 0.15 eq.), and then the mixture was stirred at 35 °C overnight. TLC (PE/EA = 6/1) showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. The residue was partitioned between EA (100 mL) and water (150 mL) and the aqueous layer was extracted with EA (100 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography, eluted by PE/EA (50/1 ~ 30/1) to give crude product, which further purified by preparative HPLC to give compound **38e-3** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 6.83 (d, *J* = 10.8 Hz, 1H), 6.71 (s, 1H), 4.13-4.08 (m, 1H), 3.84 (s, 3H), 3.82 (br, 1H), 2.34-2.30 (m, 2H), 1.84-1.66 (m, 4H).

[00758] Step 3: A mixture of compound **38e-3** (750 mg, 2.73 mmol, 1.0 eq.) in pivaloyl chloride (20 mL) was stirred at 75 °C for 1.5 h. LCMS showed that the reaction was complete. Then the mixture was concentrated under reduced pressure. The residue was purified by column chromatography, eluted by PE/EA (40/1 ~ 20/1) to give compound **38e-4** (as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 6.98 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 4.71-4.68 (m, 1H), 3.81 (s, 3H), 2.17-2.14 (m, 1H), 1.99-1.91 (m, 1H), 1.68-1.62 (m, 1H), 1.56-1.49 (m, 3H), 0.98 (s, 9H).

[00759] Step 4: To a mixture of compound **38e-4** (440 mg, 1.22 mmol, 1.0 eq.), HCOOLi (283 mg, 4.88 mmol, 4.0 eq), TEA (493 mg, 4.88 mmol, 4.0 eq.) in DMF (40 mL) was added $Pd(OAc)_2$ (24 mg, 0.12 mmol, 0.1 eq.) and Xantphos (72 mg, 0.24 mmol 0.2 eq) under N_2. Ac_2O (493 mg, 4.88 mmol, 4.0 eq) was then added into the mixture under N_2. The resulting mixture was stirred at 90 °C for 2 h. TLC (PE:EA = 3:1) showed the reaction was complete. The mixture was poured into water (50 mL), basified to pH = 12, and washed with EtOAc (20 mL x 2). The aqueous phase was collected, acidified to pH = 3, and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4,

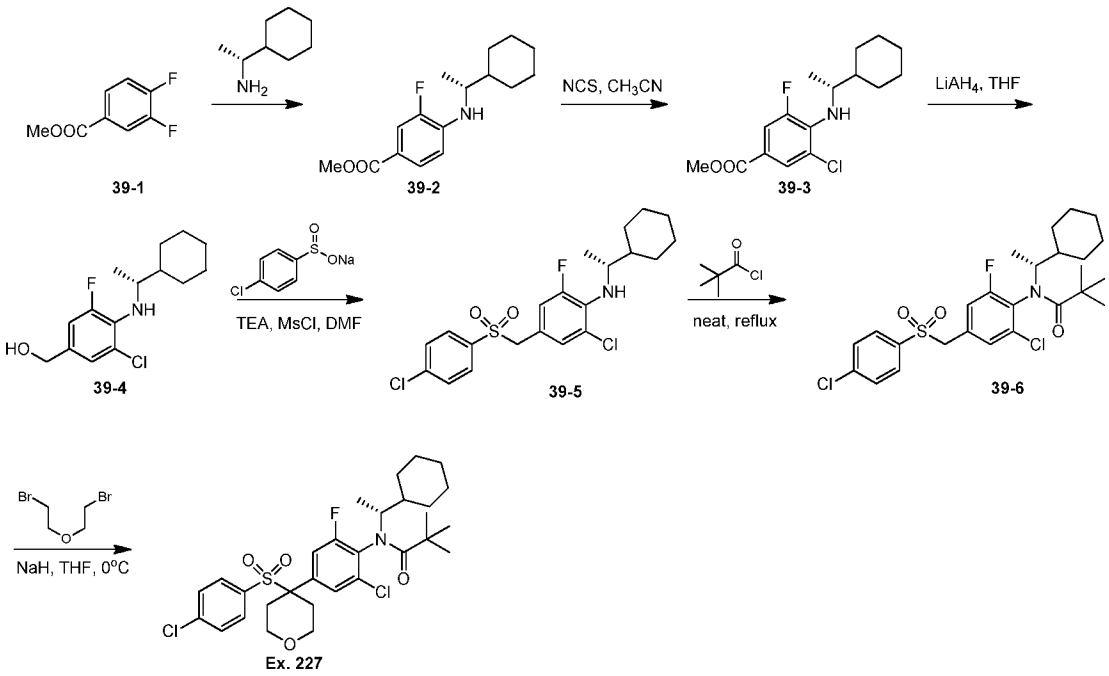
concentrated to give the crude product **38e-5** as yellow oil which was directly used in the next step without further purification.

[00760] Step 5: To a mixture of crude compound **38e-5** (394 mg, 1.22 mmol, 1.0 eq.) and K_2CO_3 (842 mg, 6.1 mmol, 5.0 eq.) in DMF (10 mL) was added CH_3I (2.0 g, 14 mmol, 11 eq.). The mixture was stirred at 30 °C for 4 h. TLC (PE/EA = 5/1) showed the reaction was complete. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 2). The combined organic layers were washed by brine (20 mL x 2) and concentrated in vacuum and the residue was purified by flash column chromatography (eluent: PE/EA = 10/1) to give the product **38e-6** as a yellow oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 8.8 Hz, 1H), 7.44 (s, 1H), 4.76-4.72 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 2.22-2.17 (m, 1H), 1.99-1.98 (m, 1H), 1.70-1.68 (m, 2H), 1.60-1.52 (m, 2H), 1.00 (s, 9H).

[00761] Example #234: was prepared as described in **Scheme 38**, using compound **38e-6** as starting material in **step 4**. ^{1}HNMR: (400 MHz, DMSO) δ: 7.35 (s, 4H), 6.61 (s, 1H), 6.55 (d, *J* = 10.4 Hz, 1H), 4.71-4.69 (m, 1H), 4.02 (d, *J* = 11.2 Hz, 2H), 3.70 (s, 3H), 3.31 (t, *J* = 11.2 Hz, 2H), 2.69 (t, *J* = 11.2 Hz, 2H), 2.31 (d, *J* = 11.2 Hz, 2H), 2.19-2.16 (m, 1H), 1.99-1.95 (m, 1H), 1.62-1.54 (m, 4H), 1.00 (s, 9H). LCMS(ESI): (M+H: 538).

[00762] PREPARATIVE EXAMPLE #227:

[00763] SCHEME 39.



[00764] Step 1: A mixture of compound **39-1** (11.4 g, 66 mmol, 1.0 eq.), DIEA (17.1 g, 132 mmol, 3.0 eq.), (*R*)-1-cyclohexylethanamine (10 g, 80 mmol, 1.2 eq.) in DMSO (150 mL)

was stirred at 120 °C for 12 h. TLC (PE:EA = 30:1) showed the reaction was complete. Then the mixture was poured into ice-water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (eluent: PE/EA = 100/1) to give target compound **39-2** as a white solid. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.70 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, *J* = 12.4 Hz , *J* = 2.0 Hz, 1H), 6.61 (t, *J* = 8.4 Hz, 1H), 4.24 (br, 1H), 3.85 (s, 3H), 3.43-3.37 (m, 1H), 2.18-1.69 (m, 5H), 1.28-1.24 (m, 1H), 1.23-1.04 (m, 8H).

[00765] Step 2: To a mixture of compound **39-2** (8.4 g, 30 mmol, 1.0 eq.) in CH_3CN (20 mL) was added NCS (6.3 g, 45 mmol, 1.5 eq.) and the mixture was stirred at 60 °C for 3 h. TLC (PE:EA = 30:1) showed the reaction was complete. The mixture was concentrated to give the crude product which was purified by column chromatography (eluent: PE/EA = 100/1) to give target compound **39-3** as a white solid. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.79 (s, 1H), 7.57 (dd, *J* = 13.6, 2.0 Hz, 1H), 4.33 (br, 1H), 3.88 (s, 3H), 3.87-3.82 (m, 1H), 1.86-1.70 (m, 5H), 1.41-1.03 (m, 9H).

[00766] Step 3: To a mixture of compound **39-3** (5.0 g, 16 mmol, 1.0 eq.) in THF (50 mL) was added LAH (1.2 g, 32 mmol, 2.0 eq.) in portions at -30 °C. The resulting mixture was stirred at this temperature for 3 h. TLC (PE:EA = 3:1) showed the reaction was complete. Then the reaction was quenched with H_2O (1.2 mL) at -30 °C, 15% aq. NaOH (1.2 mL) and H_2O (3.6 mL) were added in turn, the resulting mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated to give the crude product which was purified by flash column chromatography (eluent: PE/EA = 10/1) to give target compound **39-4** as a white solid.

[00767] ^{1}HNMR: (400 MHz, CDCl3) δ: 7.09 (s, 1H), 6.94 (dd, *J* = 12.8, 2.0 Hz, 1H), 4.55 (d, *J* = 4.4 Hz, 2H), 3.78 (br, 1H), 3.66-3.64 (m, 1H), 1.81-1.64 (m, 6H), 1.25-1.20 (m, 1H), 1.18-1.09 (m, 8H).

[00768] Step 4: To a mixture of compound **39-4** (2.8 g, 10 mmol, 1.0 eq.), sodium 4-chlorobenzenesulfinate (2.4 g, 12 mmol, 1.2 eq.) and TEA (2.0g, 20 mmol, 2.0 eq.) in DMF (50 mL) was added methanesulfonyl chloride (1.7 g, 15 mmol, 1.5 eq.) at ice-bath. The mixture was stirred at room temperature for 2 h. TLC (PE:EA = 3:1) showed most of compound **39-4** was consumed. Subsequently the reaction mixture was concentrated. The residue was diluted with water (40 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and further

purified by flash column chromatography (eluent: PE/EA = 5/1) to give the product **39-5** as a white solid. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.61 (d, *J* = 8.4 Hz, 2H),7.49 (m, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 6.73 (dd, *J* = 13.2, 2 Hz, 1H), 4.16 (s, 2H), 3.91 (br, 1H), 3.71-3.67 (m, 1H), 1.81-1.64 (m, 5H), 1.12-1.04 (m, 9H).

[00769] Step 5: A mixture of compound **39-5** (600 mg, 1.45 mmol, 1.0 eq.) in pivaloyl chloride (10 mL) was stirred at 110 °C for 12 h. LC-MS showed the reaction was complete. Then the mixture was concentrated in vacuum. The residue was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the crude product, which was purified by flash column chromatography (eluent: PE/EA =3/1) to give the product **39-6** as a white solid. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.63 (d, *J* = 8.4 Hz, 2H),7.48 (d, *J* = 8.4 Hz, 2H), 7.05 (s, 0.4H), 7.03 (s, 0.6H), 6.93 (d, *J* = 12.8 Hz, 0.6H), 6.90 (d, J = 12.8 Hz, 0.4H), 4.27 (s, 2H), 4.15-4.13 (m, 1H), 1.89-1.62 (m, 6H), 1.30-0.88 (m, 17H).

[00770] Step 6: To a mixture of compound **39-6** (500 mg, 0.95 mmol, 1.0 eq.) and NaH (151 mg, 3.79 mmol, 4.0 eq., 60% dispensed in mineral oil) in THF (20 mL) was added 1-bromo-2-(2-bromoethoxy)ethane (551 mg, 2.37 mmol, 2.5 eq.) at room temperature. The resulting mixture was stirred at 75 °C for 12 h. LC-MS showed the reaction was complete. The reaction was then quenched with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). Then combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: Agella Venusil ASB C18 150 x 21.2 mm x 5um; Detection wavelength: 220 nm) to give **Example # 227** as a white solid. ^{1}HNMR: (400 MHz, CDCl3) δ: 7.39-7.30 (m, 4H), 7.09 (s, 0.4H), 7.06 (s, 0.6H), 7.01 (d, *J* = 11.2 Hz, 0.6H), 6.98 (d, *J* = 11.2 Hz, 0.4H), 4.11-4.05 (m, 0.6H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.85-3.78 (m, 0.4H), 3.29 (t, *J* = 11.2 Hz, 2H), 2.66-2.59 (m, 2H), 2.30 (d, *J* = 13.2 Hz, 2H), 1.92-1.75 (m, 6H), 1.19-0.99 (m, 17H). LCMS (ESI): (M+H: 598).

[00771] Example #228: was prepared as described in **Scheme 39**, using cyclopropanecarbonyl chloride in **step 5**.

^{1}HNMR: (400 MHz, CDCl3) δ: 7.54 (d, J = 8.4 Hz, 2H), 7.44-7.37 (m, 4H), 4.40-4.36 (m, 0.6H), 4.18-4.13 (m, 0.4H), 3.89 (d, J = 11.6 Hz, 2H), 3.18 (t, J = 12.4 Hz, 2H), 2.52 (d, J = 1.6 Hz, 2H), 2.50-2.31 (m, 2H), 1.77-1.41 (m, 6H), 1.09-0.68 (m, 14H). LCMS (ESI): (M+H: 582).

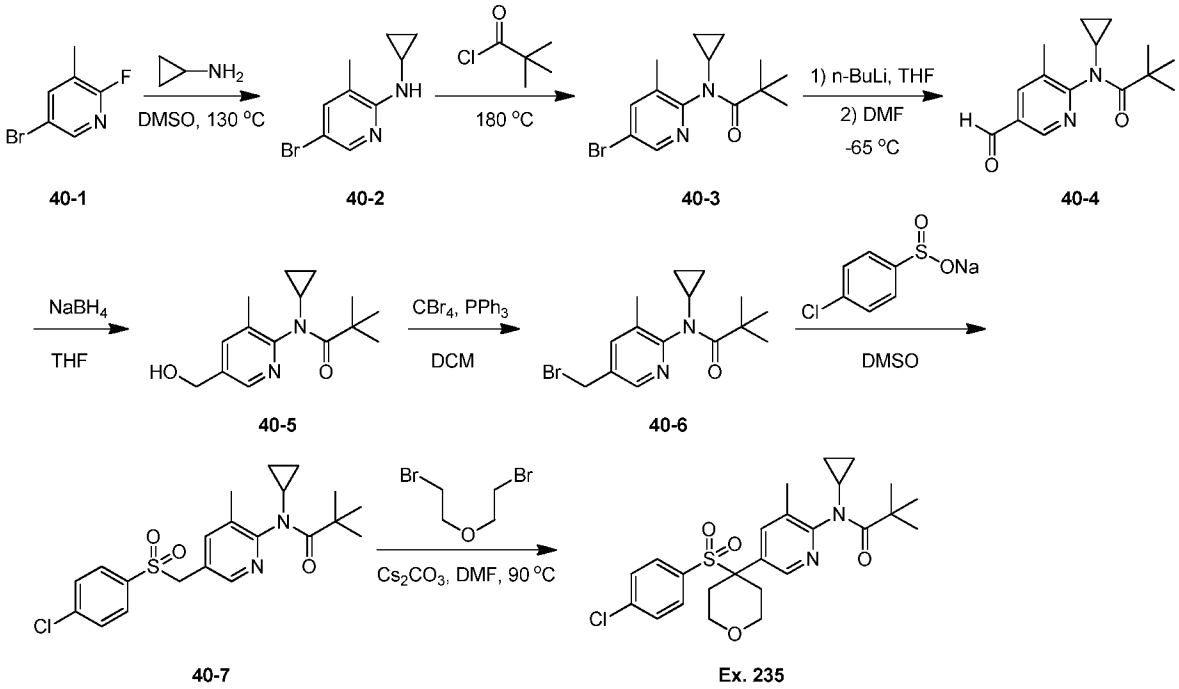
[00772] Example #229: was prepared as described in **Scheme 39**, using (*S*)-1-

cyclohexylethanamine in **step 1**.

^{1}HNMR: (400 MHz, CDCl3) δ: 7.39-7.30 (m, 4H), 7.09 (s, 0.4H), 7.06 (s, 0.6H), 7.01 (d, J = 11.2 Hz, 0.6H), 6.98 (d, J = 11.2 Hz, 0.4H), 4.11-4.05 (m, 0.6H), 4.04 (d, J = 12.0 Hz, 2H), 3.85-3.78 (m, 0.4H), 3.29 (t, J = 11.2 Hz, 2H), 2.66-2.59 (m, 2H), 2.30 (d, J = 13.2 Hz, 2H), 1.92-1.75 (m, 6H), 1.19-0.99 (m, 17H). LCMS (ESI): (M+H: 598).

[00773] PREPARATIVE EXAMPLE #235:

[00774] SCHEME 40.



[00775] Step 1: A solution compound **40-1** (6.0 g, 32 mmol, 1.0 eq.) and cyclopropanamine (5.5 g, 96 mmol, 3.0 eq.) in DMSO (30 mL) was heated at 130 °C overnight. TLC (PE/EA = 10/1) showed that most of compound **40-1** was consumed. The mixture was cooled to room temperature, poured into water (120 mL) and then extracted with PE/EA (4/1, 50 mL x 2). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (30/1 ~ 10/1) to give compound **40-2** as an oil. ^{1}HNMR: (400 MHz, DMSO) δ: 7.99 (s, 1H), 7.41 (s, 1H), 6.27 (s, 1H), 2.71-2.65 (m, 1H), 2.25 (s, 3H), 0.67-0.64 (m, 2H), 0.48-0.46 (m, 2H).

[00776] Step 2: A mixture of compound **40-2** (1.2 g, 5.3 mmol, 1.0 eq.) in pivaloyl chloride (12 mL) was stirred at 180 °C for 10 h. The reaction was performed in two batches. TLC (PE/EA = 6/1) showed that the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography, eluted with PE/EA

(25/1 ~ 15/1) to give compound **40-3** as a yellow oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 8.08 (s, 1H), 3.12-3.08 (m, 1H), 2.21 (s, 3H), 0.98 (s, 9H), 0.71-0.68 (m, 2H), 0.27-0.24 (m, 2H).

[00777] Step 3: To a solution of compound **40-3** (2.4 g, 7.7 mmole, 1.0 eq.) in dry THF (40 mL) was added dropwise n-BuLi (7.7 mL, 19.3 mmol, 2.5 eq. 2.5 M in n-hexane) at -65 ~ -60 °C under N_2, and then the mixture was stirred at -65 °C for 20 min. To the mixture was added dropwise dry DMF (2 mL), and then the mixture was stirred -65 °C for 1 h. TLC (PE/EA = 2/1) showed that the reaction was complete. The mixture was quenched with water (5 mL) at -60 ~40 °C under stirring. Then the mixture was allowed to warm to room temperature, diluted with water (50 mL) and extracted with EA (30 mL x3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (5/1) to give compound **40-4** as a yellow oil.

[00778] ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 10.10 (s, 1H), 8.77 (s, 1H), 8.06 (s, 1H), 3.18-3.16 (t, 1H), 2.34 (s, 3H), 1.24 (s, 9H), 0.80-0.79 (m, 2H), 0.43-0.42 (m, 2H).

[00779] Step 4: To a solution of compound **40-4** (0.91 g, 3.5 mmol, 1.0 eq.) in dry THF (8 mL) was added in portions $NaBH_4$ (0.29 g, 7.7 mmol, 2.2 eq.) under ice-water bath, and then the mixture was stirred at room temperature for 1 h. TLC (PE/EA = 1/1) showed that the reaction was complete. The mixture was quenched with water (20 mL) under ice-water bath and then extracted with EA (15 mL x 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (1/1 ~ 1/5) to give compound **40-5** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 8.24 (s, 1H), 7.63 (s, 1H), 4.73 (s, 2H), 3.16-3.14 (m, 1H), 2.27 (s, 3H), 1.01 (s, 9H), 0.78-0.72 (m, 2H), 0.47-0.43 (m, 2H).

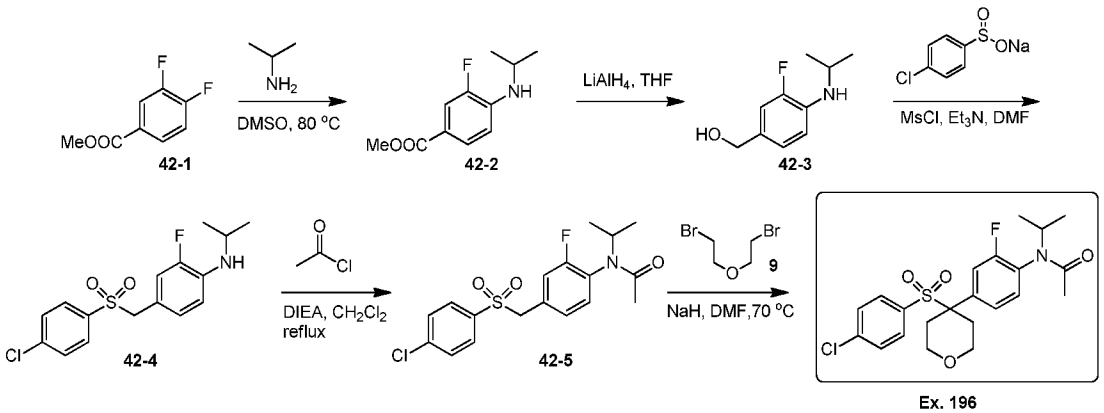
[00780] Step 5: To a solution of compound **40-5** (0.42 g, 1.6 mmol, 1.0 eq.) in dry DCM (10 mL) were added PPh_3 ((0.63 g, 2.4 mmol, 1.5 eq.) and CBr_4 (0.80 g, 2.4 mmol, 1.5 eq) under ice-water bath, and then the mixture was stirred at room temperature for 1.5 h under N_2. TLC (PE/EA = 1/1) showed that the reaction was complete. The mixture was concentrated in vacuum and the residue was purified by column chromatography, eluted with PE/EA (6/1) to give compound **40-6** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 8.31 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 4.46 (s, 2H), 3.17-3.13 (m, 1H), 2.28 (s, 3H), 1.06 (s, 9H), 0.78-0.73 (m, 2H), 0.45-0.42 (m, 2H).

[00781] **Step 6:** A mixture of compound **40-6** (0.41 g, 1.3 mmol, 1.0 eq.) and sodium 4-chlorobenzenesulfinate (0.28 g, 1.4 mmol, 1.1 eq.) in DMSO (6 mL) was stirred at 60 °C for 1 h. TLC (PE/EA = 2/1) showed that the reaction was complete. The mixture was cooled to room temperature, poured into ice-water (40 mL) under stirring. The solid formed was filtered, washed with water (5 mL x 2), and then dissolved in EA (40 mL). The solution obtained was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by re-crystallization from PE/EA (12 mL/3 mL) to give **40-7** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.56 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 4.30 (s, 2H), 3.15-3.11 (m, 1H), 2.26 (s, 3H), 1.04 (s, 9H), 0.77-0.73 (m, 2H), 0.37-0.32 (m, 2H).

[00782] **Step 7:** To a solution of compound **40-7** (0.25 g, 0.6 mmol, 1.0 eq.) in dry DMF (8 mL) were added Cs_2CO_3 (0.59 g, 1.8 mmol, 3.0 eq.) and bis(2-bromoethyl) ether (0.42 g, 1.8 mmol, 3.0 eq.), and then the mixture was stirred at 90 °C for 2 days. LCMS showed that all compound **7** was converted into target product. The mixture was cooled to room temperature, diluted with water (30 mL) and extracted with EA (20 mL x 3), washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography, eluted with PE/EA (3/1 ~ 1/1) to give the crude product, which was further purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: Synergi 150 x 30 mm; Detection wavelength: 220 nm) to afford **Example # 235** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 8.14 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.05-3.97 (m, 2H), 3.87-3.82 (m, 1H), 3.25 (s, 2H), 2.57-2.38 (m, 4H), 2.30 (s, 3H), 1.51 (s, 9H), 1.13-1.12 (m, 2H), 0.73-0.70 (m, 2H). LCMS(ESI): (M+Na: 513).

[00783] **PREPARATIVE EXAMPLE #196:**

[00784] **SCHEME 42.**



[00785] **Step 1:** To a mixture of compound **42-1** (10 g, 58 mmol, 1.0 eq.) in DMSO (20 mL) was added DIEA (15 g, 116 mmol, 2.0 eq.) and isopropylamine (3.4 g, 69 mmol, 1.2 eq.). The mixture was stirred at 70°C for 3 days. TLC (PE:EA = 30:1) showed the starting material was consumed completely. Then the reaction mixture was poured into ice water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (eluent: PE/EA = 30:1) to give target compound **42-2** as a white solid.

[00786] ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.72 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 6.63 (t, J = 8.4 Hz, 1H), 4.35 (br, 1H), 3.88 (s, 3H), 3.76-3.65 (m, 1H), 1.26 (d, J = 6.4 Hz, 6H).

[00787] **Step 2:** To a mixture of compound **42-2** (2.10 g, 0.01 mol, 1.0 eq.) in THF (150 mL) was added LAH (0.76 g, 0.02 mol, 2.0 eq.) in portions at -30°C. The resulting mixture was stirred at 0 °C for 2 h. TLC (PE:EA = 3:1) showed the starting material was consumed completely. Then the reaction was quenched by careful addition of H_2O (0.7 mL) followed by 15% aq. NaOH (0.7 mL) and H_2O (2.1 mL). The resulting mixture was stirred at 0°C for 20 min and then filtered. The filtrate was concentrated in vacuum and the crude product was further purified by flash column chromatography (eluent: PE/EA = 3/1) to give target compound **42-3** as a colorless oil.

[00788] ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.01-6.97 (m, 2H), 6.64-6.68 (m, 1H), 4.53 (d, J = 5.2 Hz, 2H), 3.72-3.59 (m, 2H), 1.23 (d, J = 6.8 Hz, 6H).

[00789] **Step 3:** To a mixture of compound **42-3** (552 mg, 3.0 mmol, 1.0 eq.), sodium 4-chlorobenzenesulfinate (653 mg, 3.3 mmol, 1.0 eq.) and TEA (606 mg, 6.0 mmol, 2.0 eq.) in DMF (10 mL) was added methanesulfonyl chloride (513 mg, 4.5 mmol, 1.5 eq.) at 0°C. Then the mixture was stirred at room temperature for 12 h. TLC (PE:EA = 3:1) showed the starting material was consumed completely. The reaction mixture was concentrated in vacuo. The residue was diluted with water (40 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by flash column chromatography (eluent: PE/EA = 10/1) to give the product as a yellow solid.

[00790] ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.77-6.72 (m, 3H), 4.19 (s, 2H), 3.67-3.60 (m, 1H), 1.26 (d, J = 6.4 Hz, 6H).

[00791] Step 4: To a mixture of compound **42-4** (400 mg, 1.17 mmol, 1.0 eq.) in DCM (10 mL) was added DIEA (296 mg, 2.3 mmol, 2.0 eq.) and acetyl chloride (358 mg, 4.68 mmol, 4.0 eq.). The mixture was refluxed for 12 h. LCMS showed the starting material was consumed completely. The reaction mixture was quenched with water (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the crude product, which was purified by flash column chromatography (eluent: PE/EA = 10/1) to give the product as a yellow solid. LCMS(ESI): 17642-37-3b (M+H: 384).

[00792] Step 5: To a mixture of compound **42-5** (0.24 g, 0.63 mmol, 1.0 eq.) and NaH (100 mg, 2.52 mmol, 4.0 eq., 60% dispensed in mineral oil) in DMF (20 mL) was added 1-(2-bromoethoxy)-2-bromoethane (291 mg, 1.26 mmol, 2.0 eq.) at room temperature. The resulting mixture was stirred at 70°C for 12 h. LCMS showed the starting material was consumed. Then the mixture was cooled to room temperature, poured into H_2O (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: Synergi 150*30mm; Detection wavelength: 220 nm) to give the desired pure compound **Example# 196** as white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.35-7.29 (m, 4H), 7.13-7.08 (m, 3H), 5.03-5.00 (m, 1H), 4.03 (d, *J* = 11.2 Hz, 2H), 3.33 (t, *J* = 11.2 Hz, 2H), 2.70-2.62 (m, 2H), 2.37 (d, *J* = 13.6 Hz, 2H), 1.80 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 5.6 Hz, 3H). LCMS(ESI): 17642-40-2B (M+H: 454).

[00793] Example # 197 was prepared as described in **Scheme 42**, except using 4 isobutyryl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.29 (m, 4H), 7.11-7.07 (m, 3H), 5.02-4.99 (m, 1H), 4.03 (d, *J* = 11.2 Hz, 2H), 3.35 (t, *J* = 11.2 Hz, 2H), 2.68 (t, *J* = 11.2 Hz, 2H), 2.37 (d, *J* = 13.6 Hz, 2H), 2.13 (m, 1H), 1.12-1.08 (m, 6H), 1.02-0.99 (m, 6H). LC-MS: M/Z = 482 $[M+H]^+$.

[00794] Example 198: was prepared as described in **Scheme 42**, except using cyclopropanecarbonyl chloride in **step 4.** ^{1}H NMR (400 MHz, DMSO) δ = 7.50 (d, J = 7.2 Hz, 2H), 7.34-7.24 (m, 3H), 7.23 (d, J = 7.6 Hz, 1H), 4.82-4.74 (m, 1H), 3.91-3.88 (m, 2H), 3.18-3.12 (m, 2H), 2.62-2.53 (m, 2H), 2.38-2.32 (m, 2H),), 1.17-0.86 (m, 7H), 0.84-0.55 (m, 4H). LC-MS: M/Z = 480 $[M+H]^+$.

[00795] Example #199: was prepared as described in **Scheme 42**, except using 1-methylcyclopropanecarbonyl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCL_3$) δ = 7.36-7.30

(m, 4H), 7.16-7.07 (m, 2H), 7.04–7.02 (m, 1H), 4.91-4.85 (m, 1H), 4.05-3.95 (m, 2H), 3.34-3.28 (m, 2H), 2.70-2.63 (m, 2H), 2.342.17 (m, 2H), 1.15-0.93 (m, 11H), 0.42-0.35 (m, 2H). LC-MS: M/Z = 494 $[M+H]^+$.

[00796] Example #200: was prepared as described in **Scheme 42**, except using 3,3-difluorocyclobutanecarbonyl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCL_3$) δ = 7.39 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.15-7.08 (m, 3H), 5.01-4.94 (m, 1H), 4.04 (d, J = 11.6 Hz, 2H), 3.32 (t, J = 11.6 Hz, 2H), 2.92-2.89 (m, 2H), 2.68-2.65 (m, 2H), 2.51-2.50 (m, 1H), 2.39-2.35 (m, 4H), 1.12 (d, J = 7.2 Hz, 3H), 1.02 (d, J=7.2 Hz, 3H). LC-MS: M/Z = 552 $[M+H]^+$.

[00797] Example #201: was prepared as described in **Scheme 42**, except using 3,3-dimethylbutanoyl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCL_3$) δ: 7.36-7.30 (m, 4H), 7.11-7.02 (m, 3H), 5.04-5.00 (m, 1H), 4.03 (d, J = 11.8 Hz, 2H), 3.35 (t, J = 11.8 Hz, 2H), 2.68 (t, J = 11.8 Hz, 2H), 2.35 (d, J = 14.0 Hz, 2H), 1.91-1.82 (m, 2H), 1.12 (d, J = 6.8 Hz, 3H), 0.98 (m, 12H). LC-MS: M/Z = 510 $[M+H]^+$.

[00798] Example #202: was prepared as described in **Scheme 42**, except using 1-methyl-1H-pyrazole-4-carbonyl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCL_3$) δ: 7.47-7.39 (m, 4H), 7.31-7.26 (m, 2H), 7.14-7.12 (m, 2H), 6.77 (br. 1H), 5.12-5.09 (m, 1H), 4.01 (d, J = 9.6 Hz, 2H), 3.79 (s, 3H), 3.31 (t, J = 11.2 Hz, 2H), 2.57 (t, J = 11.2 Hz, 2H), 2.37 (d, J = 13.6 Hz, 2H) 1.22-1.12 (m, 6H). LC-MS: M/Z = 520 $[M+H]^+$.

[00799] Example #203: was prepared as described in **Scheme 42**, except using nicotinoyl chloride in **step 4.** ^{1}H NMR (400 MHz, CD_3OH) δ: 8.88 (s, 1H), 8.80 (s, 1H), 8.40 (s, 1H), 7.90 (s, 1H), 7.53-7.51 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.17 (m, 2H), 5.12-5.01 (m, 1H), 3.93-3.90 (m, 2H), 3.12-3.01 (m, 2H), 2.46-2.41 (m, 4H), 1.39 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H). LC-MS: M/Z = 517 $[M+H]^+$.

[00800] Example #204: was prepared as described in **Scheme 42**, except using picolinoyl chloride in **step 4.** ^{1}H NMR (400 MHz, CD_3OH) δ: 8.31 (s, 1H), 7.80 (s, 1H), 7.53-7.23 (m, 7H), 7.02-6.98 (m, 2H), 5.03-4.99 (m, 1H), 3.89-3.78 (m, 2H), 3.31-3.30 (m, 2H), 2.44-2.33 (m, 4H), 1.33 (d, J = 6.4 Hz, 3H), 1.20 (s J = 6.4 Hz, 3H). LC-MS: M/Z = 517 $[M+H]^+$.

[00801] Example #205: was prepared as described in **Scheme 42**, except using isonicotinoyl chloride in **step 4.** ^{1}H NMR (400 MHz, CD_3OH) δ: 8.75 (d, J = 4.0 Hz, 2H), 7.87 (d, J = 4.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.47-7.45 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.18-7.15 (m, 2H), 5.07-5.03 (m, 1H), 3.91-3.85 (m, 2H), 3.12-3.01 (m, 2H), 2.46-2.41 (m, 4H), 1.39 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 6.4 Hz, 3H). LC-MS: M/Z = 517 $[M+H]^+$.

[00802] Example #206: was prepared as described in **Scheme 42**, except using 6-methylpicolinoyl chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59-7.54 (m, 1H), 7.49-7.48 (m, 1H), 7.25-7.20 (m, 5H), 7.04-7.03 (m, 1H), 6.91-6.84 (m, 2H), 5.14-5.11 (m, 1H), 3.97-3.95 (m, 2H), 3.21-3.15 (m, 2H), 2.56 (m, 2H), 2.31-2.24 (m, 5H), 1.31 (d, J = 6.4 Hz, 1H), 1.22 (d, J = 6.4 Hz, 1H). LC-MS: M/Z = 531 $[M+H]^+$.

[00803] Example #207: was prepared as described in **Scheme 42**, except using (1S,2S,4R)-bicyclo[2.2.1]heptane-2-carbonyl chloride in **step 4.** ^{1}H NMR (400 MHz, DMSO) δ: 7.55-7.51 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.18 (m, 3H), 4.79-4.71 (m, 1H), 3.94-3.91 (m, 2H), 3.21-3.13 (m, 2H), 2.50 (m, 1H), 2.44-2.38 (m, 4H), 2.19-2-16 (m, 1H), 1.91-1.04 (m, 16H). LC-MS: M/Z = 534 $[M+H]^+$.

[00804] Example #208: was prepared as described in **Scheme 42**, except using Boc-chloride in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.08-7.04 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 4.57-4.53 (m, 1H), 3.98 (d, J = 11.8 Hz 2H), 3.30 (t, J = 11.8 Hz, 2H), 2.65 (t, J = 11.8 Hz, 2H), 2.32 (d, J = 13.6 Hz, 2H), 1.40 (s, 9H), 1.19-1.09 (m, 6H). LC-MS: M/Z = 534 $[M+Na]^+$.

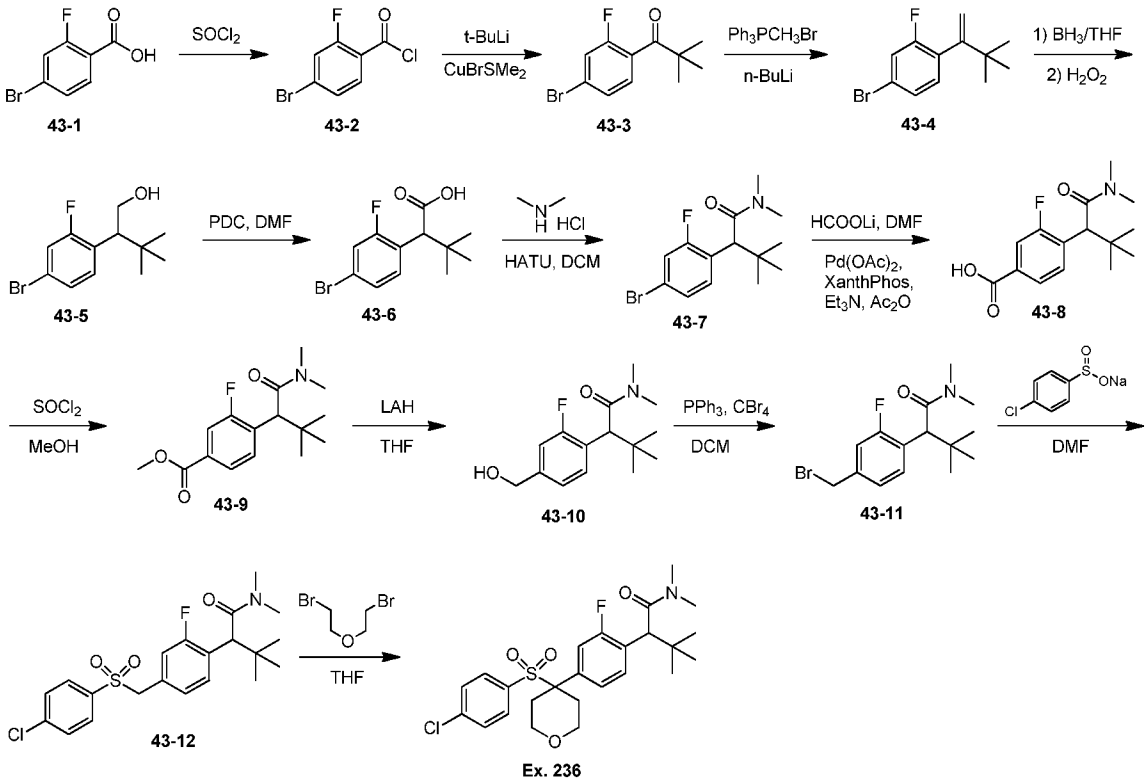
[00805] Example #238: was prepared as described in **Scheme 42**, except using methyl chloroformate in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.08-7.04 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 4.57-4.53 (m, 1H), 3.98 (d, J = 11.8 Hz 2H), 3.70 (s, 3H), 3.30 (t, J = 11.8 Hz, 2H), 2.65 (t, J = 11.8 Hz, 2H), 2.32 (d, J = 13.6 Hz, 2H), 1.19-1.09 (m, 6H). LC-MS: M/Z = 469 $[M+Na]^+$.

[00806] Example #239: was prepared as described in **Scheme 42**, except using ethyl chloroformate in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.08-7.04 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 4.57-4.53 (m, 1H), 4.05 (m, 2H), 3.98 (d, J = 11.8 Hz 2H), 3.70 (s, 3H), 3.30 (t, J = 11.8 Hz, 2H), 2.65 (t, J = 11.8 Hz, 2H), 2.32 (d, J = 13.6 Hz, 2H), 1.30-1.05 (m, 9H). LC-MS: M/Z = 506 $[M+Na]^+$.

[00807] Example #240: was prepared as described in **Scheme 42**, except using isopropyl chloroformate in **step 4.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.08-7.04 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 5.05-4.95 (m, 1H), 4.57-4.53 (m, 1H), 4.05 (m, 2H), 3.98 (d, J = 11.8 Hz 2H), 3.70 (s, 3H), 3.30 (t, J = 11.8 Hz, 2H), 2.65 (t, J = 11.8 Hz, 2H), 2.32 (d, J = 13.6 Hz, 2H), 1.30-1.05 (m, 12H). LC-MS: M/Z = 520 $[M+Na]^+$.

[00808] PREPARATIVE EXAMPLE #236:

[00809] SCHEME 43.



43-1 43-2 43-3 43-4 43-5 43-6 43-7 43-8 43-9 43-10 43-11 43-12 Ex. 236

Step 1: To a mixture of **43-1** (22 g, 160 mmol, 1.0 eq.) in $SOCl_2$ (300 mL) was added DMF (1 mL). The mixture was heated to reflux overnight and then concentrated in vacuum to give the crude product **43-2** which was directly used in the next step without further purification.

Step 2: To a mixture of $CuBr.SMe_2$ (22.6 g, 110 mmol, 1.1 eq.) in THF (800 mL) was added dropwise *t*-BuLi (1.3 M in hexane, 90 mL, 110 mmol, 1.1 eq.) at -78 °C under N_2, and the mixture was stirred at -78 °C for 30 min. Then, a solution of crude **43-2** (25 g, 100 mmol, 1.0 eq.) in THF (200 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 2 h, and then quenched with saturated aqueous NH_4Cl (1 L) and extracted with MTBE (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product which was purified by flash column chromatography (eluent: PE) to give **43-3** as colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.35-7.30 (m, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 1.26 (s, 9H).

[00810] Step 3: To a mixture of methyl triphenylphonium bromide (41.3 g, 0.116 mol, 2.0 eq.) in THF (200 mL) at -78 °C was added dropwise n-BuLi (2.5 M in hexane, 46 mL, 0.116 mol, 2.0 eq.) under nitrogen. The mixture was allowed to stir at 0 °C for 30 min, and then re-cooled to -78 °C. To the reaction mixture was added dropwise a solution of compound **43-3** (15 g, 0.058 mol, 1.0 eq.) in THF (50 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous NH_4Cl (300 mL) was added to quench the reaction and the mixture was extracted with MTBE (200 mL x 2). The combined

organic layers were washed with brine (200 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography (eluent: PE) to give the product **43-4** as a colorless oil. ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.23-7.21 (m, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 4.83 (s, 1H), 1.10 (s, 9H).

[00811] Step 4: To a mixture of compound **43-4** (7.0 g, 27 mmol, 1.0 eq.) in THF (200 mL) at 0 °C BH_3 (1.0 M in THF, 270 mL, 270 mmol, 10.0 eq.) was added dropwise. The reaction mixture was allowed to warm to room temperature, and stirred for 1 h. 1 M aq. NaOH solution (67 mL) and H_2O_2 (30% wt. in H_2O, 9.18 g, 270 mmol, 10.0 eq.) was slowly added. The reaction mixture was stirred at room temperature for 1 h, and then partitioned between MTBE (300 mL) and H_2O (300 mL). The aqueous layer was extracted with MTBE (100 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated to give crude product **43-5**, which was directly used in the next step without purification.^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.29-7.23 (m, 2H), 7.17-7.15 (m, 1H), 4.08-3.94 (m, 2H), 3.65 (t, *J* = 6.8 Hz, 1H), 3.12 (br, 1H), 0.93 (s, 9H).

[00812] Step 5: To a mixture of **43-5** (7.0 g, 0.025 mol, 1.0 eq.) in DMF (500 mL) at room temperature was added PDC (47.9 g, 0.127 mol, 5.0 eq.) in portions. The mixture was stirred at this temperature for 16 h, and then diluted with EtOAc (300 mL), filtered through a celite pad. The filtrate was washed with H_2O (200 mL x 2) and brine (200 mL), dried with Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash column chromatography (eluent: PE:EA = 10:1) to give **43-6** (2.0 g, 27%) as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.59 (t, *J* = 8.0 Hz, 1H), 7.27-7.24 (m, 2H), 3.93 (s, 1H), 1.02 (s, 9H).

[00813] Step 6: To a mixture of **43-6** (1.0 g, 3.47 mmol, 1.0 eq.) in DMF (10 mL) at room temperature was added dimethylamine hydrochloride (0.34 g, 4.14 mmol, 1.2 eq.), DIEA (1.34 g, 10.47 mmol, 3.0 eq.) and HATU (1.9 g, 5.2 mmol, 1.5 eq.). The resulting mixture was stirred at room temperature overnight. TLC (PE:EA = 4:1) showed the reaction was complete. The mixture was poured into H_2O (50 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give **43-7**. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.63 (t, *J* = 8.4 Hz, 1H), 7.28-7.24 (m, 2H), 4.10 (s, 1H), 2.98 (s, 3H), 2.90 (s, 3H), 1.04 (s, 9H).

[00814] Step 7: To a mixture of **43-7** (1.0 g, 3.16 mmol, 1.0 eq.), HCOOLi (733 mg, 12.64 mmol, 4.0 eq), TEA (1.27 g, 12.64 mmol, 4.0 eq.) in DMF (40 mL) was added $Pd(OAc)_2$ (63 mg, 0.32 mmol, 0.1 eq.) and Xantphos (189 mg, 0.63 mmol 0.2 eq.) under N_2. Ac_2O (1.27 g, 12.64 mmol, 4.0 eq.) was then added into the mixture under N_2. The resulting mixture was

stirred at 90 °C overnight. TLC (PE:EA = 3:1) showed the reaction was complete. The mixture was poured into water (50 mL), basified to pH = 12 by solid NaOH, and washed with EtOAc (20 mL x 2). The aqueous phase was acidified to pH = 3 by 3M aq. HCl, and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated to give the crude **43-8** as a yellow oil which was directly used in the next step without further purification.

[00815] ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.84-7.83 (m, 2H), 7.77-7.75 (m, 1H), 4.21(s, 1H), 4.01 (d, *J* = 12.0 Hz, 2H), 3.00 (s, 3H), 2.93 (s, 3H), 1.04 (s, 9H).

[00816] **Step 8:** To a mixture of crude compound **43-8** (660 mg) in MeOH (10 mL) was added dropwise $SOCl_2$ (1 mL). The resulting mixture was stirred at reflux overnight. TLC (PE:EA = 2:1) showed the reaction was complete, After evaporation to remove the solvent, the residue was dissolved in EA (10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give the crude product which was purified by column chromatography (eluent: PE/EA = 10/1) to give the product **43-9** as an oil.

[00817] ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.82-7.71 (m, 3H), 4.20 (s, 1H), 3.93 (s, 3H), 2.99 (s, 3H), 2.93 (s, 3H), 1.06 (s, 9H).

[00818] **Step 9:** To a mixture of **43-9** (240 mg, 0.88 mmol, 1.0 eq.) in THF (10 mL) was added LAH (67 mg, 1.76 mmol, 2.0 eq.) in portions at -30 °C. The resulting mixture was stirred at this temperature for 3 h. TLC (PE:EA = 30:1) showed the reaction was complete. Then the reaction was quenched by slow addition of H_2O (0.1 mL) at -30 °C, 15% aq. NaOH (0.1 mL) and H_2O (0.3 mL) were added in turn, the resulting mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated to give the crude product **43-10** as a white solid, which was directly used in the next step without further purification. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.66 (t, *J* = 8.0 Hz, 1H), 7.12-7.09 (m, 2H), 4.70(s, 2H), 4.12 (s, 1H), 3.76-3.60 (m, 1H), 2.98 (s, 3H), 2.91 (s, 3H), 1.05 (s, 9H).

[00819] **Step 10:** To a mixture of compound **43-10** (220 mg, 0.786 mmol, 1.0 eq.) in DCM (20 mL) was added PPh_3 (309 mg, 1.180 mmol, 1.5 eq.) and CBr_4 (394 mg, 1.18 mmol, 1.5 eq.) under N_2. The mixture was stirred at room temperature for 4 h. TLC (PE:EA = 3:1) showed the reaction was complete. Then the mixture was concentrated to give the residue. The residue was purified by column chromatography (eluent: PE/EA = 10/1) to give **43- 11** as an oil.

[00820] ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.70 (t, *J* = 8.0 Hz, 1H), 7.15-7.10 (m, 2H), 4.47 (s,

2H), 4.14 (s, 1H), 3.00 (s, 3H), 2.92 (s, 3H), 1.05 (s, 9H).

[00821] Step 11: To a mixture of **43-11** (65 mg, 0.20 mmol, 1.0 eq.) in DMF (5 mL) was added sodium 4-chlorobenzenesulfinate (47 mg, 0.24 mmol, 1.2 eq.). The mixture was stirred at room temperature for 3 h. TLC (PE:EA = 3:1) showed the reaction was complete. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give **43-12** (60 mg) as a white solid.

[00822] LCMS (ESI): (M+H: 426).

[00823] Step 12: To a mixture of **43-12** (60 mg, 0.14 mmol, 1.0 eq.) and NaH (22 mg, 0.56 mmol, 4.0 eq., 60% dispensed in mineral oil) in THF (10 mL) was added 1-bromo-2-(2-bromoethoxy)ethane (82 mg, 0.35 mmol, 2.5 eq.) at room temperature. The resulting mixture was stirred at 75 °C for 12 h. TLC (PE:EA = 3:1) showed the reaction was complete. The reaction was then quenched with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). Then combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by preparative HPLC (Mobile phase A: water with 0.05% HCl, Mobile phase B: acetonitrile; Column: synergi Max-RP 150 x 30 mm x 4 um; Detection wavelength: 220 nm) to give **Example #236** as a white solid. ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.66 (t, *J* = 8.0 Hz, 1H), 7.29-7.22 (m, 4H), 7.04 (dd, *J* = 10.0 Hz, 1.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 4.16 (s, 1H), 3.99-3.96 (m, 2H), 3.36 (t, *J* = 11.6 Hz, 1H), 3.03 (s, 3H), 2.94 (s, 3H), 2.59 (t, *J* = 4.0 Hz, 2H), 2.37-2.32 (m, 2H), 1.05 (s, 9H). LCMS(ESI): (M+H: 496).

[00824] Example #237: was prepared as described in **Scheme 43**, except using pyrrolidine in **step 6.** ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 7.82 (t, *J* = 8.0 Hz, 2H), 7.31-7.25 (m, 4H), 7.05 (d, *J* = 10.4 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.03-3.98 (m, 3H), 3.61-3.53 (m, 2H), 3.42-3.32 (m, 4H), 2.64 (t, *J* =11.6 Hz, 2H), 2.39 (t, *J* =10.0 Hz, 2H), 2.09-1.84 (m, 4H), 1.07 (s, 9H).

LCMS(ESI): (M+H: 522).

[00825] Assay 1: Biochemical GST-RORγ TR-FRET assay

[00826] Assay 1 is a method that measures the disruption or activation of co-activator peptide/RORγ binding by quantifying the ability of molecules to inhibit or enhance the activity of RORγ.

[00827] RORγ TR-FRET Assay Reagents

Name	Units/Amount	Source	Catalog Number	Storage
Biotin-TRAP220	(500 μM)	Anaspec	Custom Biotin-PVSSMAGNTKNHPMLMNLLKDNPAQ	-80 °C
GST-RORγ (LBD)	(14.74μM)	Biogen Idec.	In-house	-80 °C
DMSO	100%	Fisher	D128-500	RT
Streptavidin Allophycocyanin (SA-APC)	13.7uM SA (2.15 mg/ml)	Prozyme	PJ25S	4 °C, in the dark
Lance Eu-W1024 Anti GST	473μg/ml (2.96μM)	Perkin Elmer	AD0254	4 °C

[00828] RORγ TR-FRET Assay Buffer Components

Master Buffer	Storage
20 mM Tris-HCl, 60 mM NaCl, 5 mM $MgCl_2$, pH 7.0	Room temperature
1M Dithiothreitol (DTT), (1mM final)	-20 °C in aliquots of 100 μL
10% BSA, (0.1% final)	4 °C

[00829] Equipment and Materials:

Polypropylene 384 well plate for 100% DMSO serial dilutions	Corning 3657
120 μL Polystyrene 384 well plate for compound 1:100 buffer dilution	Greiner Bio-one 781101
70 μL, black, round well, 384 Polystyrene assay plate	Thermo Fisher, No. 95040020
Plate Reader	Analyst AD, LJL BioSystems, or PerkinElmer Envision

[00830] Final conditions for RORγ FRET Assay: (20 μL of compound + 5 μL of detection mix = 25 μL total assay volume): 20 mM Tris-HCl pH 7.0, 60 mM NaCl, 5 mM $MgCl_2$, 1mM DTT, 0.1%BSA; 10 nM GST-RORγ (LBD); 400nM Biotin-TRAP220; 50nM SA-APC; 1.5nM Eu-Anti GST IgG; 1.0% DMSO.

[00831] Assay Protocol:

[00832] Compound dilutions were prepared (125x final test concentrations) by making a 6.25 mM dilution from a 10 mM stock using 100% DMSO. Three-fold dilutions of the compounds were then prepared for nine points beyond the 6.25 mM starting concentration (6.25, 2.083, 0.6944, 0.2315, 0.0772, 0.0257, 0.00857, 0.00286, 0.00095, and 0.00032 mM). For example, 15 μL of 10 mM of the compound was added into 9 μL of DMSO, and 10 μL of

the resulting solution was titrated into 20 µL of DMSO. A 5x detection mix was prepared to the required volume (5 µL/reaction well + overage) by adding 5x the final concentrations of GST-ROR-gamma, Eu-Anti GST antibody, Biotin-TRAP220, and SA-APC in assay buffer containing 1% DMSO. Five µL per well of the 5x detection mix was added to a black 384 well assay plate. Then, 1 µL of 125x of the test compound in 100% DMSO was added into 99 µL of assay buffer in the compound buffer dilution greiner plate to result in a final DMSO concentration of 1%. Assay controls (0% inhibition and 100% inhibition controls) were added into columns 1,12, 13, and 24 of the 384 well dilution greiner plate. For the 0% inhibition control, 1 µL of 100% DMSO was added into 99 µL of assay buffer. For the 100% inhibition control,1 µL of 3.125 mM T0901317 (125x 25 µM final concentration) was added. The compound was mixed and 20 µL of the compound was transferred to the assay plate containing 5 µL of 5x detection mix. The plate was shaken for one minute, centrifuged at 1000 rpm for 10 seconds, incubated at room temperature for 60 minutes, and read on a plate reader. The LJL Analyst settings were as follows: Ratio: acceptor/donor; Acceptor: HRTF(Packard); Excitation: Europium FRET 330nm; Emission: FRET acceptor 665nm; Donor: HRTF(Packard); Excitation: Europium FRET 330nm; Emission: FRET chelate donor; Flashes/well: 100; Intergration time: 400 µs; Interval between: 1x10 ms flashes; Delay after flash: 50 µs.

[00833] Data analysis:

[00834] The RORγ FRET assay is an end point assay with a readout (emission ratio) of acceptor/donor*1000. The assay dose response testing is performed in duplicate points per concentration, with ten dilution concentrations per compound curve. The conversion of raw data to % Activity is performed using assay controls, where 100% Activity is represented by the average DMSO controls. Zero percent Activity is the average of the 25 µM, T0901317 compound controls. IC curve fitting is performed using graphpad prism, and fitting to the sigmoidal dose-response (variable slope) equation as follows:

$$Y=Bottom + (Top-Bottom)/(1+10^((Log_{EC50}-X)*HillSlope));$$

where X is the logarithm of concentration and Y is the response (Y begins at the Bottom and goes to Top with a sigmoid shape, which is identical to the "four parameter logistic equation")

[00835] In the final assay plate setup, there were sixteen compounds per 384 well plate. The DMSO controls (0% Inhibition) were in columns 1 and 13. The 25 µM T0901317 controls (100% Inhibition) were in columns 12 and 24. The compound titrations were in columns 2-

11, 14-23. Ten-point IC_{50} curves were generated with n=2 per concentration.

[00836] Assay 2: Protocol of the ROR Gal4 cellular reporter assay 293T cells

[00837] Cell Cultivation.

Cell Line Name	293T
Tissue	Embryonal kidney
Organism	Homo sapiens
Order ID (Supplier)	ACC 635 (DSMZ)
Cell doubling time	About 24-30 hours
Cell number per flask	Cells are harvested at 80-90% confluency; about 15 M io cells per T75 flask
Origin	Highly transfectable derivative of the human primary embryonal kidney cell line 293 (ACC 305) carrying a plasmid containing the temperature sensitive mutant of SV-40 large T-antigen (tsA 1609); cells were described to express SV-40 large T at 33 °C, but not at 40 °C
Reference	Pear et al. Proc. Natl. Acad. Sci. USA 90:8392-8396 (1993)
Morphology	Fibroblastoid cells growing adherently as a monolayer
Incubation	At 37 °C with 5% CO_2
Subculture	Split confluent culture 1:8 to 1:12 every 3-4 days using PBS (detach without using trypsin/EDTA, cells can be detached by tapping the flask)

[00838] Cells were used for transactivation assays following 2 to 3 passages after thawing from liquid nitrogen. The freeze medium was culture medium supplemented with DMSO to 10%. The routine culture includes two weekly passages. The cells were discarded after 4-6 weeks in assay production. For transactivation assay purposes, the cells were grown to subconfluence (80-90%).

[00839] Subcultivation of 293T cells. Cells were seeded in a T75 cm^2 flask in 20 mL of culture medium by adding 50 mL of FBS, 5 mL of Glutamax, 5 mL of NEAA, 5 mL of Sodium Pyruvate, and 5 mL of Pen/Strep to a 500 mL MEM bottle (with phenol red). The cells were grown at 37°C in the presence of 5% CO_2 until they reached subconfluence (80-90%), at which point the culture medium was discarded. PBS (about 5 mL per flask) was added to the flask at room temperature, and the cells were detached by tapping the flask. The viable cells were counted, the desired number of cells was transferred into a new flask, and the volume of the new flask was completed with new culture medium (final volume: 20 mL in a T75 cm^2 flask). The flasks were incubated at 37°C under 5% of CO_2.

[00840] Performance of the ROR Gal4 cellular reporter assays. On Day 1, cells were seeded in 96 well plates in plating medium (MEM w/o phenol red, 10% CCDS). On Day 2, the plating medium was removed and the cells were transfected. About 4-6 hours after

transfection, assay medium (MEM without phenol red and serum) was added, and then the compounds were added. On Day 3, the cells were lysed, luciferase buffers were added, and luminescence was measured in a dual-flash procedure.

[00841] Seeding cells. For each assay point, 50,000 293T cells per well of a 96 well white walled, clear bottom assay plate were used. Cells were plated in plating medium by adding 50 mL of CCDS, 5 mL of Glutamax, 5 mL of NEAA, 5 mL of Sodium Pyruvate, and 5 mL Pen/Strep to a 500 mL MEM bottle (without phenol red). Trypsinate cells were used for plating to ensure reproducibility of the process. After one washing step with about 10 mL of PBS, 1.5 mL of Trypsin-EDTA solution (Sigma-Aldrich; T3924) was added. After 2 to 3 minutes, the flask was tapped and 8 mL of culture medium was added. The cells were spun down for 2 minutes at 200xg, the supernatant was discarded, and the cells were resuspended in a small volume by pipetting the suspension up and down more than 10 times. As cells tend to form clumps, special care must be taken to separate cells from each other. Cells were then counted and plated with 50,000 cells per well in 100 µL plating medium. The 96 well assay plates were incubated overnight at 37 °C with 5% CO_2 in a humidified atmosphere.

[00842] Transfection. The transfection was carried out using a PEI solution generated at Phenex, with 71 ng total DNA per well (50 ng of nuclear receptor expressing plasmid plus 20 ng of pFR-Luc reporter and 0.5 ng of pRL-CMV reporter for each well). The DNA:PEI-solution ratio is 1:5 (µg:µL), with a PEI concentration of 0.45 µg/µL, and a DNA:PEI ratio of 1:2.25 (µg/µg).

[00843] The DNA solution was prepared by diluting the DNA in OptiMEM and gently vortexing. Enough solution should be prepared for 15µL of DNA mix per well. For the experiments described herein, a 16% excess was used. For example, for one assay plate, 2.24 µg of Firefly Luciferase reporter plasmid (pFR-Luc), 5.6 µg of NR expression vector (pCMV-BD-nuclear receptor), and 56 ng of Renilla Luciferase reporter plasmid was used. These DNA amounts were diluted in 1680 µL OptiMEM.

[00844] The PEI-solution was prepared by diluting the PEI in the same volume of OptiMEM. The amount of PEI-solution was calculated using the following formula: µg of DNA x 5. For the experiments described herein, a 16% excess was used. For example, for one assay plate, 39.8 µL of PEI-solution was diluted in 1640 µL of OptiMEM.

[00845] The transfection mix was generated by immediately adding the PEI-solution to the plasmid solution (the plasmid solution was not added to the PEI-solution), vortexing gently, and incubating the resulting solution for a minimum of 20 minutes at room temperature.

[00846] The plating medium is removed from the cells by dumping the plate and tapping dry on paper towels.

[00847] The transfection mix (PEI + DNA) was added to the adherent cells. The 96 well assay plates were incubated for 4-6 hrs at 37 °C with 5% CO_2 in a humidified atmosphere.

[00848] Compound treatment and enzyme activity measurement. The master DMSO compound plate was made by diluting the compounds from the 10 mM stock in column 11, and then diluting in a ratio of 1:3 across the plate to column 4. Column 3 contained DMSO only (high control), and column 3 contained 2.5 mM Tularik control (low). The compounds were at 1000X.

[00849] To a new 96-well plate, 132 µL of plating media (with CCDS) was added to every well. Then, 1 µL was transferred from each well of the DMSO compound plate to the corresponding well of the new dilution plate. The DMSO concentration was 7.5% and the compounds were 7.5X. The plate was covered and mixed on a plate shaker. About 4-6 hours after adding the transfection solution, 100 µL of assay medium was added to the cells. The assay medium was prepared by adding 5mL of Glutamax, 5 mL of NEAA, 5 mL Sodium Pyruvate, and 5 mL Pen/Strep to a 500ml MEM bottle (w/o phenol red). Exactly 20 µL of the compounds from the new dilution plate were added to the cells in triplicate. Although all of the wells on the edge of plate were excluded from analysis due to edge effects, they should all contain the same final volume of media: 150µL (1.3% CCDS, 0.1% DMSO and 1X compound). The cells were incubated at 37 °C with 5% CO_2 in a humidified atmosphere for 16 to 20 hours. After the incubation, the medium was completely removed by dumping and tapping the plate dry on paper towels. Exactly 20 µL of 1x Passive Lysis Buffer (Promega) was added and the plates were incubated at room temperature on a plate shaker for 10-15 min.

[00850] The measurement was performed using a BMG LUMIstar OPTIMA luminescence plate reader. First, 75 µL per well of Firefly luciferase buffer was injected. Exactly 1.1 seconds after the start of the Firefly buffer injection, 75 µL per well of Renilla luciferase buffer was injected. The complete measurement time was 2 seconds per well. For the direct firefly measurements, the average of the values 7-11 (0.6 to 1 sec) was used. For the direct renilla measurements, the average of the values 16-20 (1.5 to 1.9 sec) was used.

[00851] Materials and equipment used for ROR Gal4 cellular reporter assays. All plasmids used for the transfection of 293T cells were prepared with QIAGEN Maxi, Giga or Mega Kits and were eluted and diluted with MilliQ water.

[00852] Firefly Luciferase Buffer

Name	Concentration in Measurement Buffer	Stock Concentration
Tris HCL	25 mM (pH 7.8)	1 M (pH 7.8)
EGTA	4 mM	0.25 mM
ATP	1 mM	200 mM in 0.2 M Tris-HCl pH 7.8
AMP	0.2 mM	200 mM
DTT	1 mM	100 mM
$MgSO_4$	15 mM	1 M
D-Luciferin	0.1 mM	10 mM in 0.1 M K_xPO_4 pH 5

[00853] Renilla Luciferase Buffer

Name	Concentration in Measurement Buffer	Stock Concentration
NaCl	1.1 M	5 M
Na2EDTA	2.2 mM	0.5 M (pH adjusted to 8.3 with 5 M NaOH)
KxPO4	0.22 M	1 M (pH 5.1)
BSA (fraction V)	0.44 mg/mL	10% (w/v)
NaN3	1.3 mM	1 M
Coelenterazine	2.5 µM	2.5 mM (in methanol)

[00854] Materials.

Name	Company	Cat.No
293T cells	DSMZ	ACC635
MEM (with Phenol Red)	Sigma Aldrich	M2279
MEM (without Phenol Red)	Fisher Scientific (Ivtg)	VX51200087
OptiMEM	Fisher Scientific (Ivtg)	VX31985054
FBS	Sigma Aldrich	F7542
CCDS	Perbio (HyClone)	SH30068.03
Glutamax	Invitrogen	35050038
Pen/Strep	Sigma Aldrich	P4333
Sodium Pyruvate	Sigma Aldrich	S8636
Non Essential Amino Acids (NEAA)	Sigma Aldrich	M7145
PBS	Sigma Aldrich	D8537
PEI	Sigma Aldrich	408727
DMSO	Sigma Aldrich	41648
Passive Lysis Buffer (5x)	Promega	E1941
D-Luciferine	PJK	260150
Coelentrazine	PJK	260350

EGTA	Sigma Aldrich	E3889
ATP	Sigma Aldrich	A26209
AMP	Sigma Aldrich	01930
BSA (fraction V)	Serva	11930.04
T75 Flasks	NUNC	353136
U-bottom 96 well plates	Greiner	650101
96 well assay plates	Corning	3903

[00855] Equipment.

Name	**Company**	**Type**
LUMIstar OPTIMA	BMG	(with two Reagent Injectors)
Pipetting Robot	BioTek	Precision XS

[00856] ROR-gamma has been implicated in the development and function of lymphoid tissue inducer cells, thymocytes, γδ T cells, natural killer cells, and both cytotoxic and helper αβ T cells. These cell types and soluble factors produced by these cells, including the cytokines IL-17, IL-17F and IL-26, have been demonstrated to contribute to autoimmune pathology in numerous animal models of disease and have been implicated in the pathogenesis of human immune-mediated diseases. Modulators of ROR-gamma block the development of these pathogenic cell types and the proinflamatory cytokines they produce. Such action provides therapeutic benefit to the immune mediated diseases in which these cells act.

[00857] The compounds are modulators of ROR-gamma activity against the nuclear receptor. Most of the compounds of the invention have IC_{50} values of less than 1 μM, and others have IC_{50} values as low as 0.100 μM, still others have IC_{50} values as low as 0.010 μM, as determined by the Biochemical GST-RORγ TR-FRET assay. Additional information is provided in the Table below.

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
1	E
2	C
3	D
4	E
5	D
6	E
7	C
8	E
9	D
10	C
11	B
12	C
13	D
14	C
15	D
16	D
17	C
18	D
19	D
20	A
21	D
22	D
23	C
24	E
25	D
26	D
27	C
28	E
29	E
30	C
31	A
32	D
33	A
34	D
35	A
36	C
37	A
38	C
39	A
40	C
41	D
42	D
43	E
44	A

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
45	E
46	E
47	E
48	D
49	F
50	E
51	C
52	E
53	C
54	D
55	E
56	B
57	E
58	E
59	D
60	D
61	D
62	F
63	D
64	D
65	F
66	D
67	F
68	F
69	E
70	F
71	F
72	E
73	F
74	F
75	E
76	E
77	E
78	F
79	D
80	D
81	F
82	D
83	F
84	F
85	D
86	E
87	E
88	F

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
89	E
90	E
91	E
92	E
93	F
94	E
95	D
96	D
97	F
98	F
99	C
100	E
101	E
102	A
103	E
104	E
105	E
106	D
107	D
108	D
109	E
110	C
111	C
112	C
113	E
114	D
115	E
116	E
117	F
118	E
119	E
120	E
121	E
122	D
123	E
124	E
125	D
126	D
127	D
128	D
129	C
130	D
131	D
132	C

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
133	E
134	C
135	E
136	D
137	E
138	D
139	E
140	E
141	D
142	C
143	D
144	C
145	D
146	D
147	C
148	C
149	C
150	C
151	C
152	E
153	E
154	D
155	E
156	E
157	C
158	E
159	C
160	E
161	E
162	F
163	F
164	D
165	E
166	E
167	E
168	E
169	F
170	E
171	E
172	E
173	E
174	E
175	D
176	E

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
177	F
178	E
179	F
180	E
181	E
182	E
183	E
184	D
185	C
186	D
187	D
188	D
189	C
190	C
191	D
192	D
193	A
194	C
195	D
196	D
197	E
198	E
199	E
200	D
201	F
202	C
203	D
204	E
205	C
206	D
207	E
208	F
209	D
210	E
211	E
212	E
213	F
214	E
215	C
216	E
217	E
218	D
219	D
220	E

Ex #	Fret IC_{50} (2.5nM 1XKD) (μM)
221	E
222	E
223	E
224	E
225	D
226	D
227	E
228	E
229	E
230	D
231	D
232	E
233	E
234	E
235	D
236	D
237	D
238	E
239	E
240	F

[00858] In the foregoing Table, IC_{50} data is represented as follows: greater than or equal to 20 microMolar is designated at A; less than 20 microMolar but greater than or equal to 10 microMolar is designated as B; less than 10 microMolar but greater than or equal to 1 microMolar is designated at C; less than 1 microMolar but greater or equal to 100 nanoMolar is designated as D; less than 100 nanoMolar but greater or equal to 10 nanoMolar is designated as E; and less than 10 nanoMolar is designated as F.

[00859] Assay 3: RORγ Splenocyte IL-17

[00860] Reagents and buffer used in RORγ Splenocyte IL-17 assay

Reagent Name	Source	Catalog Number	Storage
Anti-Mouse CD3e	eBioscience	14-0031	4 °C
Anti-Mouse CD28	eBioscience	14-0281	4 °C
Recombinant Human TGF-beta 1	R&D Systems	240-B	-20 °C
Recombinant Mouse IL-6	eBioscience	14-8061	-80 °C
Recombinant Mouse IL-23	eBioscience	14-8231	-80 °C
DMSO	Fisher	D128-1	RT
RPMI-1640	Biogen Idec	In house	4 °C
T0901317	CALBIOCHEM	575310	-20 °C

Buffer	Storage
Lysis buffer: Hemolytic Geys Solution (Media Prep)	4 °C
IL-17 ELISA Reagent Diluent: 1% BSA in PBS, pH7.2-7.4, 0.2uM filtered.	4 °C
Wash Buffer: 10 X PBS in 0.5% TWEEN 20	RT

[00861] Equipment and Materials.

96 Well Polypropylene Microplate for 100% DMSO serial dilutions	Greiner Bio-one, # 651201
96 Well Clear Round Bottom TC-Treated Microplate for compound 1:1000 RPMI dilution and cell culture	Corning, # 3799

96 well plate for ELISA	Costar, # 3590
Mouse IL-17 DuoSet ELISA Development kit	R & D systems, # Dy421
Microplate Spectrophotometer	SpectraMax® Plus 384
70 μm Nylon Cell Strainer	BD Falcon, # REF 352350
Centrifuge	Eppendorf, # Centrifuge 5702R
Swing-bucket rotor for Centrifuge 5702	Eppendorf, # A-4-38

[00862] Assay Protocol.

[00863] **Day -1.** The round-bottom 96 well plate (Corning, # 3799) was coated with 10 μg per mL of anti-mCD3e in PBS (50 μL per well) and stored at 4 °C overnight.

[00864] **Day 0.** The primary compound dilutions (1000x final test concentrations) were prepared in a 96 well polypropylene plate (Greiner Bio-one, # 651201) by making a 5 mM dilution from a 10 mM stock using 100% DMSO. Three-fold dilutions of the compounds were then prepared for seven points beyond the 5 mM starting concentration (5, 1.667, 0.556, 0.185, 0.062, 0.021, 0.007, and 0.002 mM). For example, 10 μL of 10 mM compound was added into 10 μL of DMSO, of which 8 μL was titrated into 16 μL of DMSO. The plate was covered and stored in a hood at room temperature.

[00865] The splenocytes were then prepared. Spleens from 3 wild type C57BL/6 mice were harvested, and then dissociated using a syringe plunger with a 70 μm cell strainer (BD Falcon, # REF 352350) on a 50 mL tube. The cells were rinsed through the strainer using about 20 mL RPMI, and then centrifuged for 5 minutes at 0.3 rcf (1300 rpm, Eppendorf, # Centrifuge 5702R, # rotor A-4-38). The supernatant was discarded. The pellet was dispersed and properly resuspended by tapping the tube and adding to the pellet 1 mL of lysis buffer per spleen. After incubation at room temperature for 5 minutes, the cells were centrifuged for 5 min at 0.3 rcf and the supernatant was discarded. The cells were resuspended in 5 mL RPMI and counted. The cell concentration was then adjusted to $5x10^6$ cells per mL. Anti-mCD3e were aspirated from the wells, and 100 μL per well of the cells were coated in a 96 well plate (Corning, #3799).

[00866] A mixture of cytokines and antibody in RPMI (5% excess) was prepared: 1 ng/mL TGF-b, 10 ng/mL IL-6, 0.625 ng/mL IL-23, 5 μg/ml anti-mCD28. To each well was added 90 μl of the cytokines antibody mixture, to result in a total volume of 190 μl per well.

[00867] Exactly 5 μL of the diluted compound was added to the 245 μL RPMI, the solution was mixed, and 10 μL was transferred to each well. The final volume for each well was 200

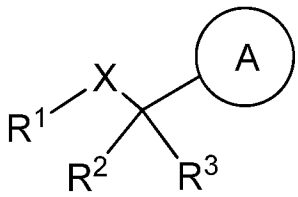
μL, resulting in a final concentration of 5, 1.667, 0.556, 0.185, 0.062, 0.021, 0.007, 0.002 μM for each compound. Control wells were prepared by adding 7 μl 100% DMSO into 343 μl RPMI for the DMSO high controls, and 2.5 μM T0901317 for the low controls (prepared by adding 4 μL of 5 mM T0901317 stock to 4 μL DMSO, mixing the solution, and then add 7 μL into 343 μl RPMI). The cells were incubated at 37 °C in CO_2 incubator for 2 days.

[00868] Day 2. The supernatant was collected at stored at -20 °C. The IL-17 cytokine level from the supernatant was then determined using the Mouse IL-17 DuoSet ELISA Development kit. Assay dose response testing was performed in triplicate points per concentration using eight dilution concentrations per compound curve. The conversion of raw data to %Activity was performed using assay controls, where 100% Activity was represented by the average DMSO controls, and 0% Activity was the average of the 2.5 μM T0901317 compound controls. EC_{50} curve fitting was performed using graphpad prism and fitting to the sigmoidal dose-response (variable slope) equation as follows: Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope)), with all of the variables as previously described.

CLAIMS

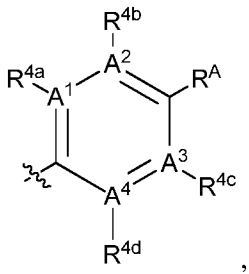
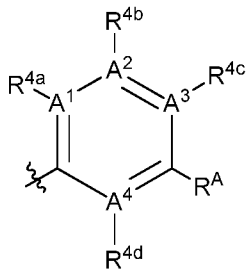
What is claimed is:

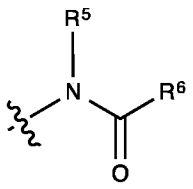
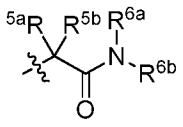
1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

A is  , or  ;

R^A is  ; or  ;

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

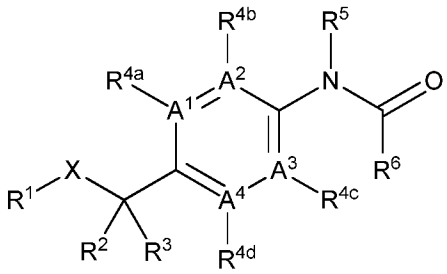
R^{5a} and R^{5b} are each independently H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl;

R^{6a} and R^{6b} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or R^{6a} and R^{6b} together form an optionally substituted heterocycloalkyl ring; or

R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring.

2. The compound of claim 1, wherein the compound of Formula I is Formula Ia:



Formula Ia

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;

A^1, A^2, A^3, and A^4 are each independently C or N;

R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form an optionally substituted carbocyclyl or an optionally substituted heterocyclyl;

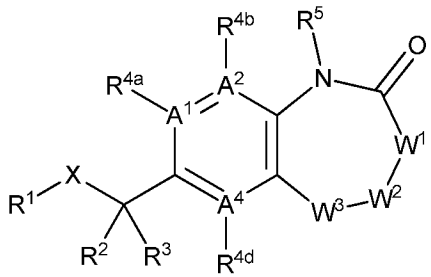
R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;

R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl;

R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring.

4. The compound of claim 2 or 3, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula Ia is Formula Ia^1:



Formula Ia^1

or a pharmaceutically acceptable salt thereof,

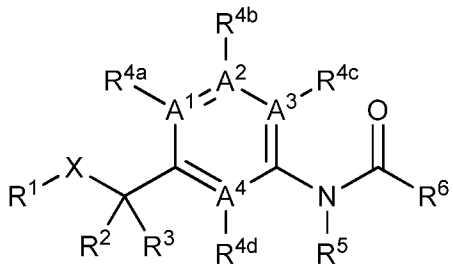
wherein:

W^1 is CR^{7a}, R^{7b}, NR^{7c}, or O;

W^2 and W^3 are each independently $CR^{7a}R^{7b}$, NR^{7c}, O, or a bond; and

R^{7a}, R^{7b}, and R^{7c} are each independently H or C_{1-4} alkyl.

5. The compound of claim 1, wherein the compound of Formula I is Formula Ib:



Formula Ib

or pharmaceutically acceptable salts thereof, wherein:

X is SO or SO_2;
A^1, A^2, A^3, and A^4 are each independently C or N;
R^1 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;
R^2 and R^3 are each independently H, optionally substituted alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted alkoxyl, amino, CN, OH, or R^2 and R^3 together form optionally substituted carbocyclyl or optionally substituted heterocyclyl;
R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, optionally substituted alkyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, halogen, amino, CN, OH, or absent when the ring atom to which they are bound is N;
R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;
R^6 is H, amino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or
R^{4c} and R^6 taken together form an optionally substituted heterocyclic ring.

6. The compound of claim 2 or 4, or 5, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein
A^1, A^2, and A^4 are each C;
A^1 and A^2 are each C, and A^4 is N;
A^1 and A^4 are each C, and A^2 is N; or
A^2 and A^4 are each C, and A^1 is N.

8. The compound of claim 7 or a pharmaceutically acceptable salt thereof, wherein X is SO_2.

9. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted carbocyclyl, and R^5 is optionally substituted alkyl, optionally substituted heterocyclyl, or optionally substituted carbocyclyl.

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, and R^{4d} are each independently H, halogen, optionally substituted alkyl or absent.

11. The compound of claim 10 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted phenyl.

12. The compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, unsubstituted or substituted with halogen.

13. The compound of claim 12 or a pharmaceutically acceptable salt thereof, wherein:
R^2 and R^3 together form optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloketonyl, optionally substituted heterocyclyl, optionally substituted spirocyclyl, or optionally substituted bicyclyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, oxo, carboxyl, acetyl, alkyl-OH, haloalkyl, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

14. The compound of claim 13 or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, or carboxyl.

15. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and
R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted alkoxyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form an optionally substituted carbocyclic ring or an optionally substituted heterocyclic ring.

17. The compound of claim 16 or a pharmaceutically acceptable salt thereof, wherein
A^1, A^2, A^3, and A^4 are each C;
A^1, A^2, and A^4 are each C, and A^3 is N;
A^1, A^3, and A^4 are each C, and A^2 is N;
A^1 and A^4 are each C and A^2 and A^3 are each N; or

A^3 and A^4 are each C and A^1 and A^2 are each N.

18. The compound of claim 17 or a pharmaceutically acceptable salt thereof, wherein X is SO_2.

19. The compound of claim 18 or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6 are each independently optionally substituted alkyl, optionally substituted carbocycle, or optionally substituted heterocyclyl.

20. The compound of claim 19 or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d} are each independently H, halo, optionally substituted alkyl or absent.

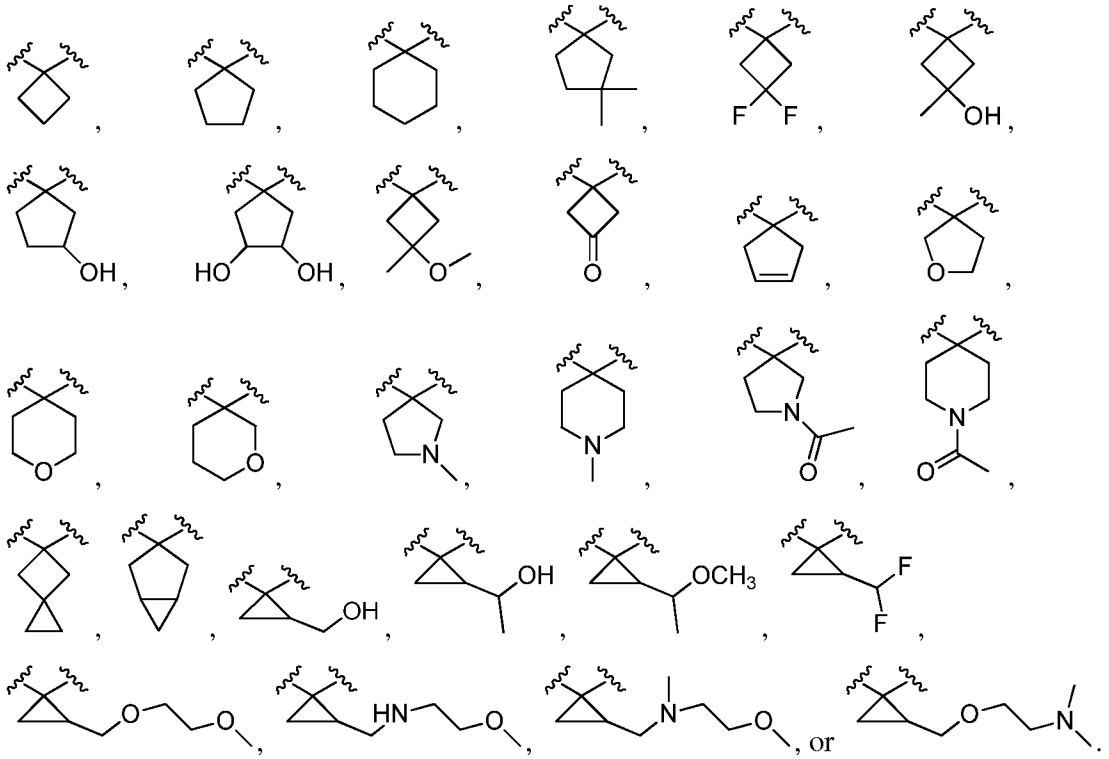
21. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted phenyl.

22. The compound of claim 21 or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, unsubstituted or substituted with halogen.

23. The compound of claim 22 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, oxo, amino, carboxyl, acetyl, alkyl-OH, haloalkyl, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

24. The compound of claim 23 or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, or carboxyl.

25. The compound of claims 1-13 or 15-23, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form a ring selected from any of the following formulas:



26. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein:
R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, oxo, amino, carboxyl, acetyl, alkyl-OH, haloalkyl, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

27. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or

more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

29. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and -(alkyl-Q)$_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

30. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form oxetane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, N-C_{1-2} alkyl azetidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylazetidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, OH, F, and Cl.

32. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclobutanone, cyclopentanone, cyclohexanone, or cycloheptanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclobutanone, cyclopentanone, or cyclohexanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

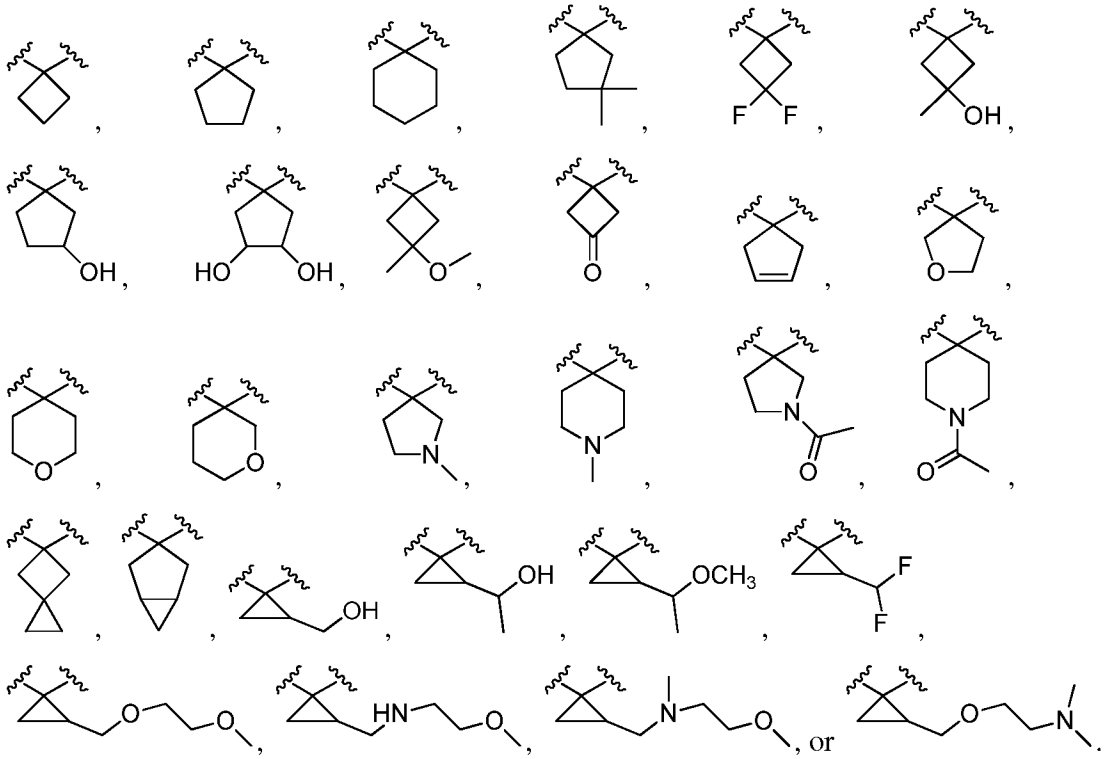
34. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[2.6]nonanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[3.6]decanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, spiro[4.6]undecanyl, spiro[5.5]undecanyl, spiro[5.6]dodecanyl, or spiro[6.6.]tridecanyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

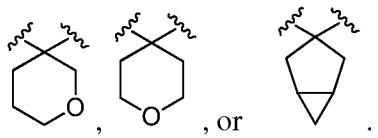
36. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[5.1.0]octyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[5.2.0]nonyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, bicyclo[5.3.0]decyl, bicyclo[4.4.0]decyl, bicyclo[5.4.0]undecyl, or bicyclo[5.5.0]dodecyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, or bicyclo[4.4.0]decyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

38. The compound of claim 6 or 26, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form:



39. The compound of any one of claims 6, 26 or 38, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form:



40. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted OC_{1-6} alkyl, CN, or OH.

41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, C_{1-4} alkyl, C_{3-6} cycloalkyl, OC_{1-4} alkyl, CN, or OH; wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and OC_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-2} alkyl, OC_{1-2} alkyl, OH, halogen, amino, and carboxyl.

42. The compound of claim 40 or 41, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, C_{1-2} alkyl, OC_{1-3} alkyl, or OH;
wherein each of the C_{1-2} alkyl and OC_{1-2} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, F, Cl, and Br.

43. The compound of any one of claims 40-42, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each CH_3.

44. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted alkyl.

45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-5} alkyl;
wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

46. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{2-6} alkenyl;
wherein the C_{2-6} alkenyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

47. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

48. The compound of claim 47, or a pharmaceutically acceptable salt thereof, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

49. The compound of claim 47 or 48, or a pharmaceutically acceptable salt thereof, wherein R^1 is cyclopentyl or cyclohexyl; wherein each of the foregoing moieties is optionally

substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, fluoroalkyl hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen.

50. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted heterocyclyl.

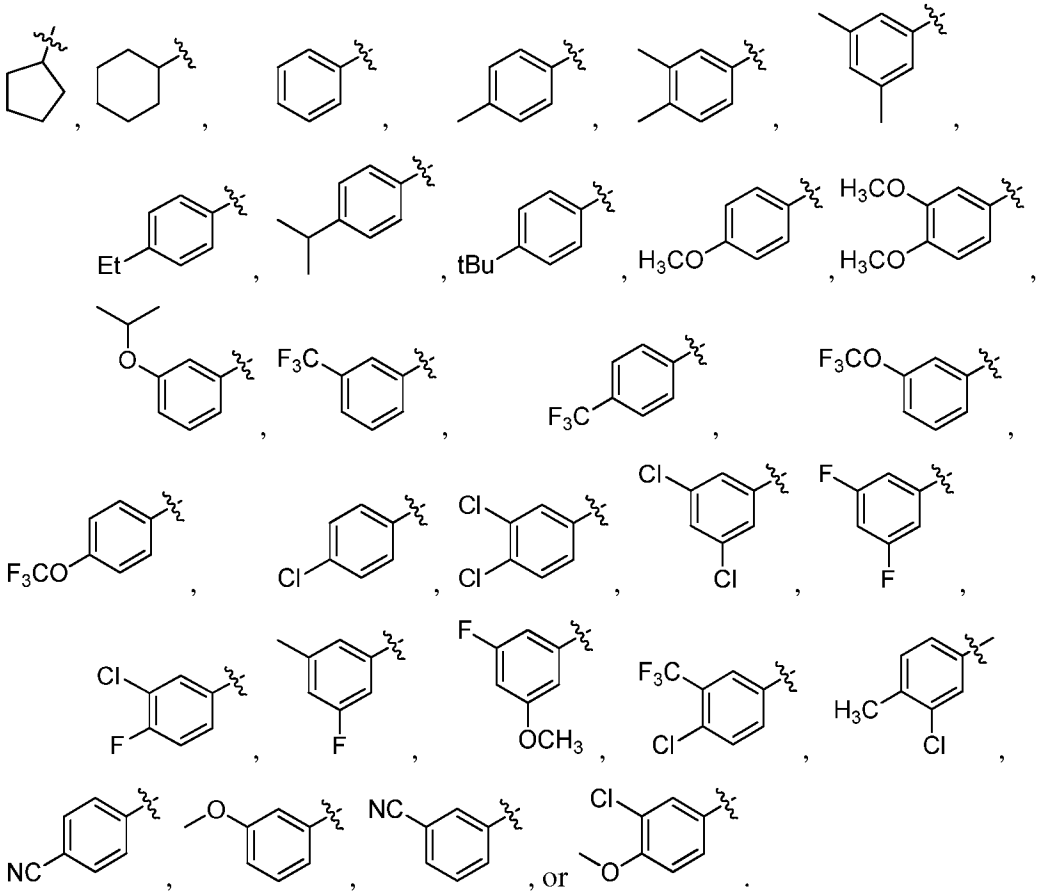
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein R^1 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

52. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted aryl or optionally substituted heteroaryl.

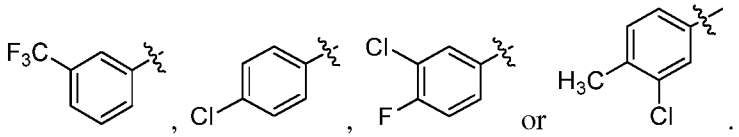
53. The compound of claim 52, or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrrole, furan, thiophene, isothiophene, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyridine, pyrimidine, or pyrazine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, cyano, alkoxyl, haloalkoxyl, carboxyl, amino, and halogen.

54. The compound of claim 52 or 53, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN.

55. The compound of any one of claims 1-10 or 26-43, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



56. The compound of any one of claims 1-10, 26-43 or 55, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



57. The compound of any one of claims 4-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:

A^1, A^2, and A^4 are each C; and

R^{4a}, R^{4b}, and R^{4d} are each H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

58. The compound of claim 57, or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, and R^{4d} are each independently C_{1-3} alkyl, OC_{1-3} alkyl, F, Cl, Br, or OH; wherein the C_{1-3} alkyl and OC_{1-3} alkyl are each optionally substituted with one or more unsubstituted

substituents selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

59. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, and R^{4d} are each independently H, CH_3, C_2H_5, OCH_3, OC_2H_5, CH_3, CF_3, OCF_3, F, Cl, or OH.

60. The compound of claim 57 or 58, or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, and R^{4d} are each H.

61. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^1 and A^2 are each C, and A^4 is N;
R^{4a} and R^{4b} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and
R^{4d} is absent.

62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

63. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^1 and A^4 are each C, and A^2 is N;
R^{4a} and R^{4d} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and
R^{4b} is absent.

64. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4d} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

65. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^2 and A^4 are each C, and A^1 is N;
R^{4b} and R^{4d} are each independently H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH; and
R^{4a} is absent.

66. The compound of claim 65, or a pharmaceutically acceptable salt thereof, wherein R^{4b} and R^{4d} are each independently H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

67. The compound of any one of claims 1-6 or 26-54, or a pharmaceutically acceptable salt thereof, wherein:
A^1 and A^2 are each N, and A^4 is C;
R^{4a} and R^{4b} are each absent; and
R^{4d} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

68. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein R^{4d} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

69. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^1 and A^4 are each N, and A^2 is C;
R^{4a} and R^{4d} are each absent; and
R^{4b} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

70. The compound of claim 69, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

71. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^2 and A^4 are each N, and A^1 is C;
R^{4b} and R^{4d} are each absent; and
R^{4a} is H, optionally substituted C_{1-4} alkyl, optionally substituted OC_{1-4} alkyl, halogen, or OH.

72. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is H, CH_3, C_2H_5, OCF_3, OCH_3, OC_2H_5, F, Cl, or OH.

73. The compound of any one of claims 1-6 or 26-56, or a pharmaceutically acceptable salt thereof, wherein:
A^1, A^2, and A^4 are each N; and
R^{4a}, R^{4b}, and R^{4d} are each absent.

74. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally

substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl.

75. The compound of claim 74, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted alkyl.

76. The compound of claim 75, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

77. The compound of claim 75 or 76, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane.

78. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

79. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

80. The compound of claim 79, or a pharmaceutically acceptable salt thereof, wherein R^5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

81. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted heterocyclyl.

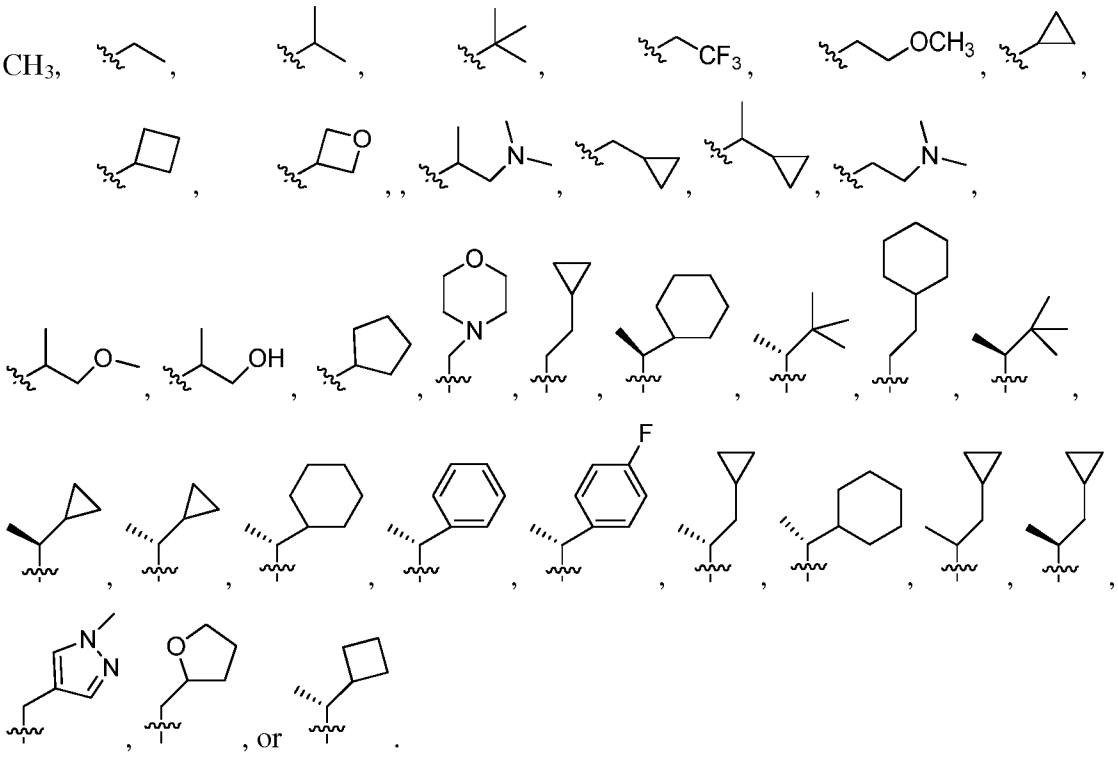
82. The compound of claim 81, or a pharmaceutically acceptable salt thereof, wherein R^5 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide,

tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

83. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted aryl or optionally substituted heteroaryl.

84. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted aralkyl or optionally substituted heteroaralkyl.

85. The compound of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein R^5 is:



86. The compound of any one of claims 4-85, or a pharmaceutically acceptable salt thereof, wherein:
W^1 is $CR^{7a}R^{7b}$, and W^2 and W^3 are each $CR^{7a}R^{7b}$ or a bond;
W^1 is O, and W^2 and W^3 are each $CR^{7a}R^{7b}$ or a bond;
W^2 is O, and W^1 and W^3 are each $CR^{7a}R^{7b}$ or a bond;

W^3 is O, and W^1 and W^2 are each $CR^{7a}R^{7b}$ or a bond; or
R^{7a} and R^{7b} are each independently H or C_{1-3}alkyl.

87. The compound of claim 86, or a pharmaceutically acceptable salt thereof, wherein:
W^1 and W^2 are each $CR^{7a}R^{7b}$;
W^3 is O; and
R^{7a} and R^{7b} are each independently H or CH_3.

88. The compound of claim 86, or a pharmaceutically acceptable salt thereof, wherein W^1 is $C(CH_3)(CH_3)$ and W^2 is CH_2.

89. The compound of any one of claims 1-86, or a pharmaceutically acceptable salt thereof, wherein X is SO.

90. The compound of any one of claims 1-86, or a pharmaceutically acceptable salt thereof, wherein X is SO_2.

91. The compound of any one of claims 1-2 or claim 5, or a pharmaceutically acceptable salt thereof, wherein:
R^{4c} is H, optionally substituted C_{1-6} alkyl, optionally substituted OC_{1-6} alkyl, optionally substituted carbocycle, halogen, CN, OH, or absent; and
R^6 is optionally substituted alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted alkoxyl, optionally substituted carbocycle, or optionally substituted heterocycle.

92. The compound of claim 91, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form an optionally substituted carbocyclic ring, or an optionally substituted heterocyclic ring.

93. The compound of claim 92, or a pharmaceutically acceptable salt thereof, wherein:
R^2 and R^3 together form cycloalkyl, cycloalkenyl, cycloketonyl, heterocyclyl, spirocyclyl, or bicyclyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, alkoxyl, OH, halogen, amino, oxo, carboxyl, acetyl, alkyl-OH, haloalkyl, and -(alkyl-$Q)_n$-alkyl, wherein each Q is independently O, NH, or N(C_{1-4} alkyl), and n is 1 or 2.

94. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

95. The compound of claim 94 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

96. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form oxetane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, N-C_{1-2} alkyl azetidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylazetidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

97. The compound of claim 96 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, N-C_{1-2} alkyl pyrrolidine, N-C_{1-2} alkyl piperidine, N-acetylpyrrolidine, or N-acetylpiperidine; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, OH, F, and Cl.

98. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclobutanone, cyclopentanone, cyclohexanone, or cycloheptanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

99. The compound of claim 98 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form cyclobutanone, cyclopentanone, or cyclohexanone; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents

selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

100. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein:
R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[2.6]nonanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[3.6]decanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, spiro[4.6]undecanyl, spiro[5.5]undecanyl, spiro[5.6]dodecanyl, or spiro[6.6.]tridecanyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

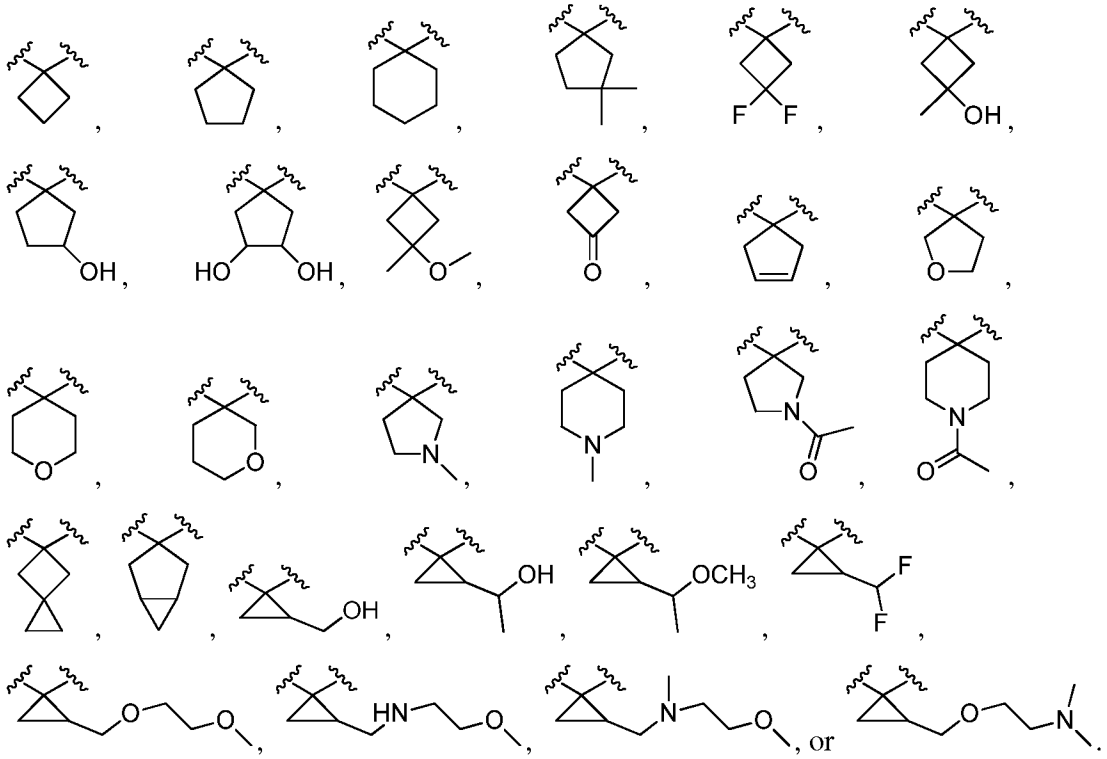
101. The compound of claim 100 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl, spiro[4.4]nonanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

102. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[5.1.0]octyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[5.2.0]nonyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, bicyclo[5.3.0]decyl, bicyclo[4.4.0]decyl, bicyclo[5.4.0]undecyl, or bicyclo[5.5.0]dodecyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, OH, F, Cl, Br, amino, and carboxyl.

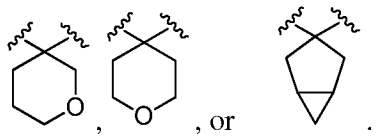
103. The compound of claim 102 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.2.0]octyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, or bicyclo[4.4.0]decyl;

wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, OC_3H_7, OH, F, Cl, and Br.

104. The compound of claim 92 or 93, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form:



105. The compound of any one of claims 92-93 or 104, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 together form:



106. The compound of claim 89 or 90, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted OC_{1-6} alkyl, halogen, CN, OH.

107. The compound of claim 106 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, C_{1-4} alkyl, C_{3-6} cycloalkyl, OC_{1-4} alkyl, halogen, CN, or OH;

wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and OC_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-2} alkyl, OC_{1-2} alkyl, OH, halogen, amino, and carboxyl.

108. The compound of claim 106 or 107, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently H, C_{1-2} alkyl, OC_{1-2} alkyl, F, Cl, Br, or OH; wherein each of the C_{1-2} alkyl and OC_{1-2} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of CH_3, OCH_3, F, Cl, and Br.

109. The compound of any one of claims 106-108 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each CH_3.

110. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted alkyl.

111. The compound of claim 110 or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-5} alkyl
optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

112. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{2-6} alkenyl
optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

113. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

114. The compound of claim 113 or a pharmaceutically acceptable salt thereof, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

115. The compound of claim 113 or 114, or a pharmaceutically acceptable salt thereof, wherein R^1 is cyclopentyl or cyclohexyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, haloalkyl, hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen.

116. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted heterocyclyl.

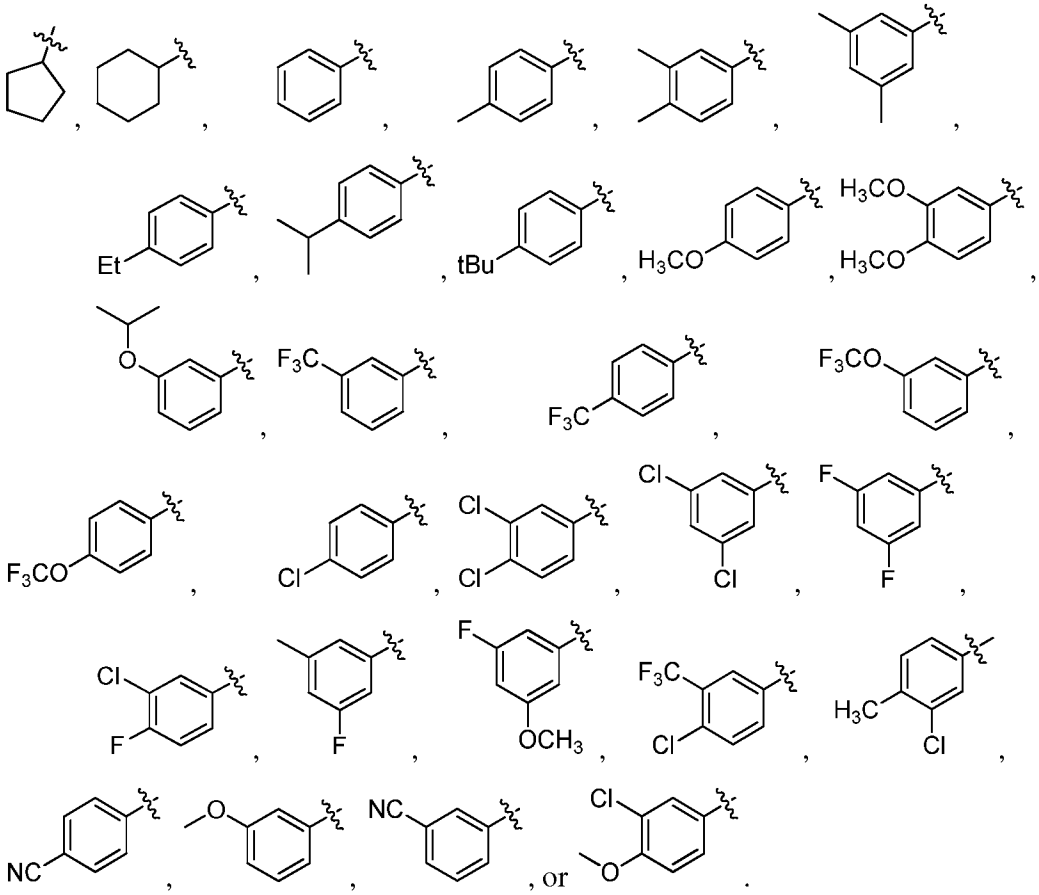
117. The compound of claim 116 or a pharmaceutically acceptable salt thereof, wherein R^1 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

118. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted aryl or optionally substituted heteroaryl.

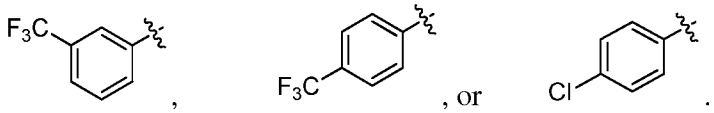
119. The compound of claim 118 or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrrolyl, furanyl, thiophenyl, isothiophenyl, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyridinyl, pyrimidinyl, or pyrazinyl;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

120. The compound of claim 118 or 119, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN.

121. The compound of any one of claims 89-109 or a pharmaceutically acceptable salt thereof, wherein R^1 is:



122. The compound of any one of claims 89-109 or 121, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



123. The compound of any one of claims 89-122 or a pharmaceutically acceptable salt thereof, wherein:

A^1, A^2, A^3, and A^4 are each C;

A^1, A^2, and A^3 are each C, and A^4 is N;

A^1, A^2, and A^4 are each C, and A^3 is N;

A^1, A^3, and A^4 are each C, and A^2 is N;

A^2, A^3, and A^4 are each C, and A^1 is N;

A^1 and A^2 are each C and A^3 and A^4 are each N;

A^1 and A^3 are each C and A^2 and A^4 are each N;

A^1 and A^4 are each C and A^2 and A^3 are each N;

A^2 and A^3 are each C and A^1 and A^4 are each N;
A^2 and A^4 are each C and A^1 and A^3 are each N; or
A^3 and A^4 are each C and A^1 and A^2 are each N;
wherein:
when A^1 is N, then R^{4a} is absent;
when A^2 is N, then R^{4b} is absent;
when A^3 is N, then R^{4c} is absent; and
when A^4 is N, then R^{4d} is absent.

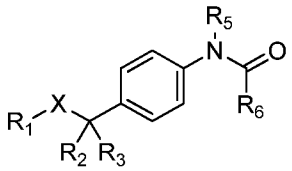
124. The compound of claim 123 or a pharmaceutically acceptable salt thereof, wherein:
A^1, A^2, A^3, and A^4 are each C;
A^1, A^2, and A^4 are each C, and A^3 is N;
A^1, A^3, and A^4 are each C, and A^2 is N;
A^1 and A^4 are each C and A^2 and A^3 are each N; or
A^3 and A^4 are each C and A^1 and A^2 are each N.

125. The compound of any one of claims 89-124 or a pharmaceutically acceptable salt thereof, wherein R^{4a}, R^{4b}, R^{4c}, and R^{4d} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, OC_{1-4} alkyl, halogen, CN, OH, or absent.

126. The compound of claim 125 or a pharmaceutically acceptable salt thereof, wherein:
R^{4a} is H, C_{1-3} alkyl, OC_{1-3} alkyl, or absent;
R^{4b} is H, C_{1-3} alkyl, OC_{1-3} alkyl, F, Cl, Br, haloalkyl, or absent;
R^{4c} is H, C_{1-3} alkyl, OC_{1-3} alkyl, or absent; and
R^{4d} is H, C_{1-3} alkyl, OC_{1-3} alkyl.

127. The compound of claim 126 or a pharmaceutically acceptable salt thereof, wherein:
R^{4a} is H, C_{1-3} alkyl, or absent;
R^{4b} is H, C_{1-3} alkyl, Cl, CF_3, or absent;
R^{4c} is H, C_{1-3} alkyl, or absent; and
R^{4d} is H or C_{1-3} alkyl.

128. The compound of any one of claims 89-127 or a pharmaceutically acceptable salt thereof, wherein the compound of Formula I comprises: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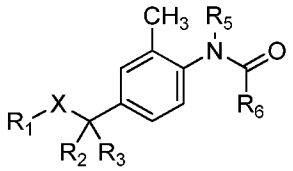
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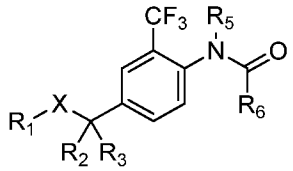
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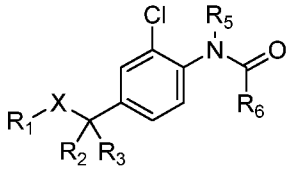
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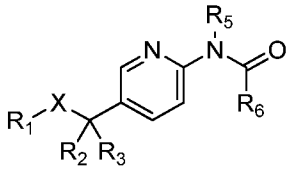
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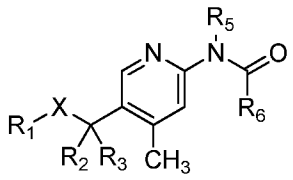
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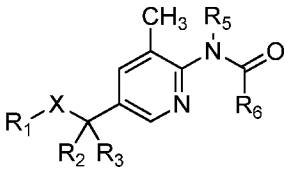
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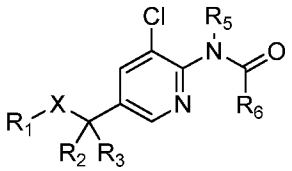
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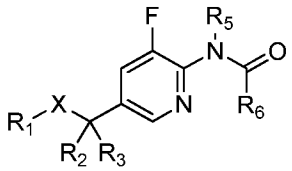
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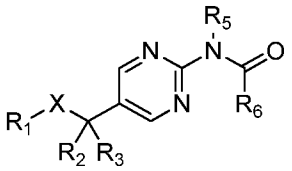

and .

129. The compound of any one of claims 89-128 or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaralkyl or optionally substituted aralkyl.

130. The compound of claim 129 or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

131. The compound of claim 129 or 130, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane.

132. The compound of any one of claims 89-128 or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

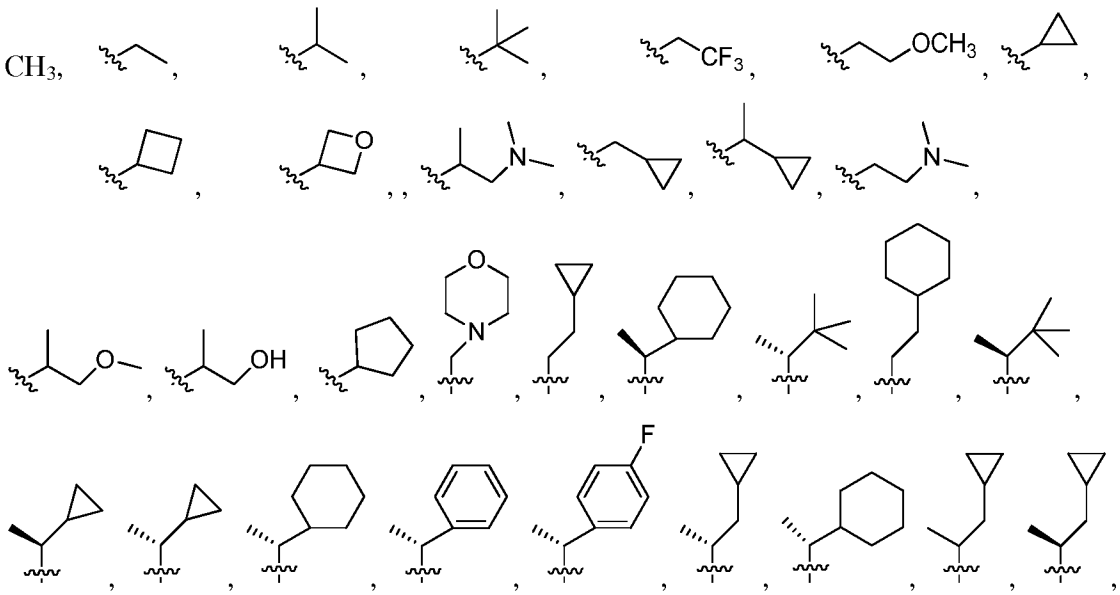
133. The compound of any one of claims 89-128 or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

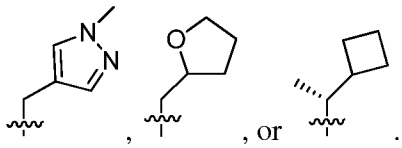
134. The compound of claim 133 or a pharmaceutically acceptable salt thereof, wherein R^5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

135. The compound of any one of claims 89-128 or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted heterocyclyl.

136. The compound of claim 135 or a pharmaceutically acceptable salt thereof, wherein R^5 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

137. The compound of any one of claims 89-128 or a pharmaceutically acceptable salt thereof, wherein R^5 is:





138. The compound of any one of claims 89-128, or a pharmaceutically acceptable salt thereof, wherein R^5 is optionally substituted aralkyl or optionally substituted heteroaralkyl.

139. The compound of claim 138, or a pharmaceutically acceptable salt thereof, wherein R^5 is aralkyl or heteroaralkyl optionally substituted with one or more unsubstituted substituents selected from the group consisting of halogen and C_{1-4} alkyl.

140. The compound of claim 89-139 or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or optionally substituted alkoxyl.

141. The compound of claim 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted alkyl.

142. The compound of claim 141 or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-5} alkyl; wherein the C_{1-5} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

143. The compound of claim 141 or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-4} alkyl; wherein the C_{1-4} alkyl is optionally substituted with one or more unsubstituted substituents selected from the group consisting of F, OC_{1-3} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and oxetane.

144. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{2-6} alkenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

145. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted cycloalkyl, or optionally substituted cycloalkenyl.

146. The compound of claim 145 or a pharmaceutically acceptable salt thereof, wherein R^6 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

147. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted heterocyclyl.

148. The compound of claim 147 or a pharmaceutically acceptable salt thereof, wherein R^6 is aziridine, oxirane, azetidine, azirine, oxetane, thietane, tetrahydrofuran, tetrahydropyran, morpholine, pyrrolidine, pyrrolidone, tetrahydrothiophene, thietane dioxide, tetrahydrothiopene dioxide, tetrahydrothiopyran dioxide, piperidine, piperidinone, piperazine, pyran, thiopyran, azepane, or azepine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

149. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted aryl or optionally substituted heteroaryl.

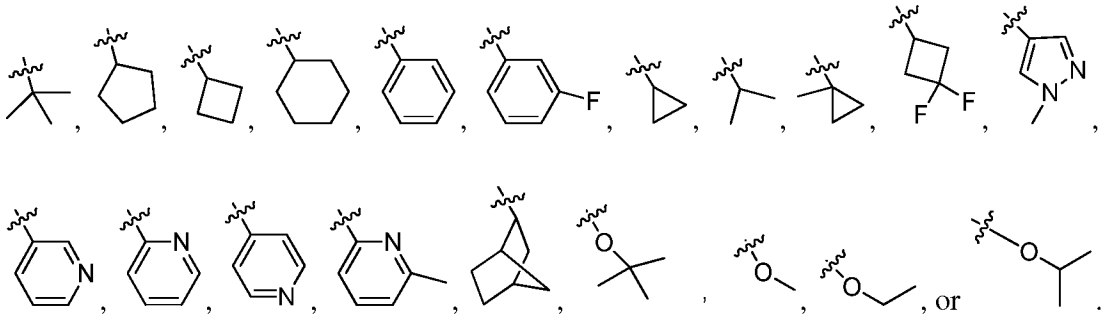
150. The compound of claim 149 or a pharmaceutically acceptable salt thereof, wherein R^6 is pyrrole, furan, thiophene, isothiophene, phenyl, indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl, pyrazole, pyridine, pyrimidine, or pyrazine;
wherein each of the foregoing moieties is optionally substituted with one or more unsubstituted substituents selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, alkoxyl, carboxyl, amino, and halogen.

151. The compound of claim 150 or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, OC_{1-4} alkyl, CF_3, OCF_3, F, Cl, and CN.

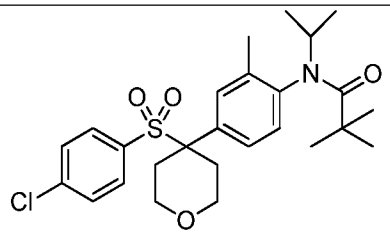
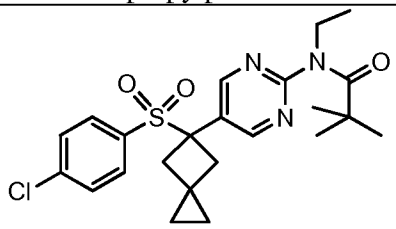
152. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is tert-butyl, cyclobutane, cyclopentane, or cyclohexane.

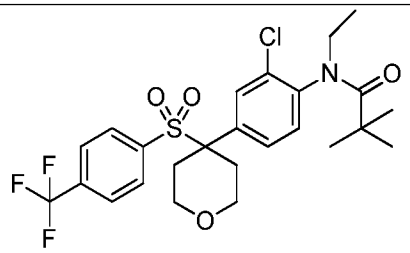
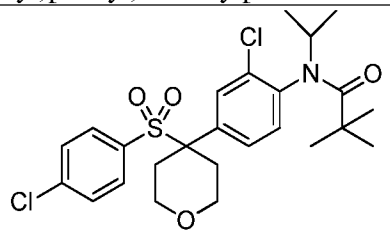
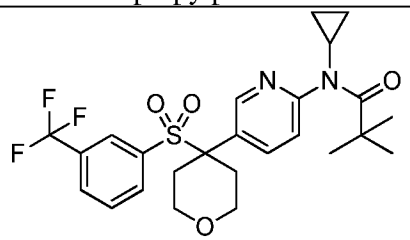
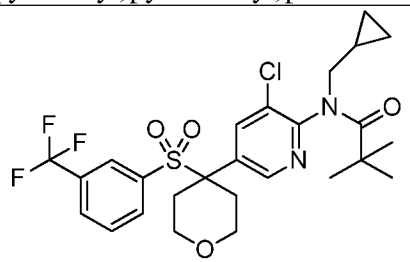
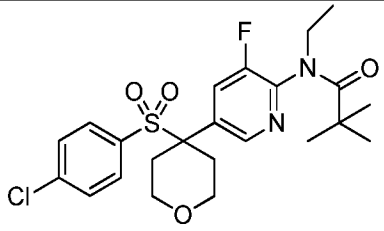
153. The compound of any one of claims 89-140 or a pharmaceutically acceptable salt thereof, wherein R^6 is alkoxyl that is optionally substituted with one or more unsubstituted substituents selected from the group consisting of C_{1-4} alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, hydroxyl, OC_{1-4} alkyl, carboxyl, amino, and halogen.

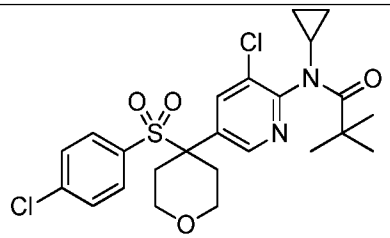
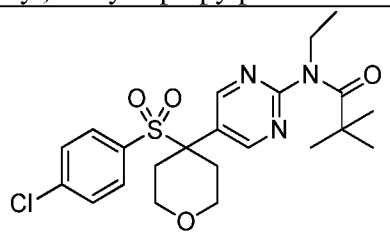
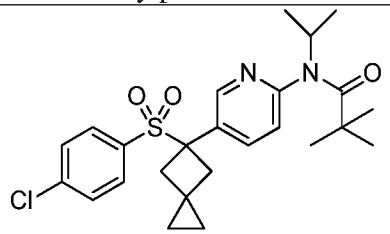
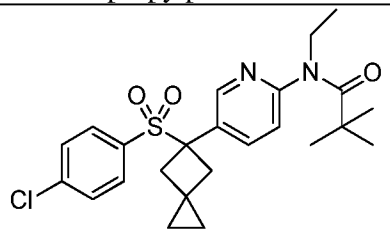
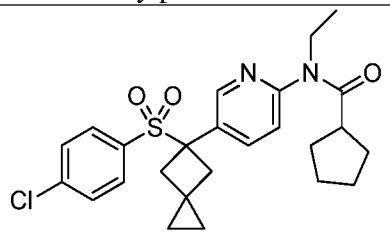
154. The compound of any one of claims 89-152, or a pharmaceutically acceptable salt thereof, wherein R^6 is:

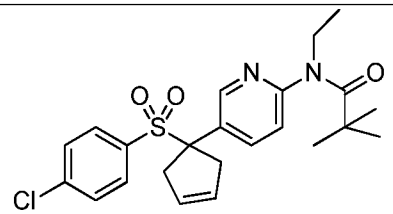
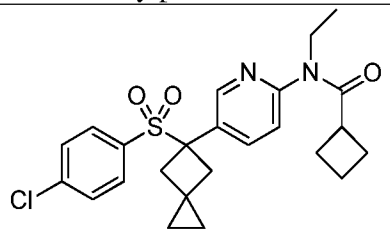
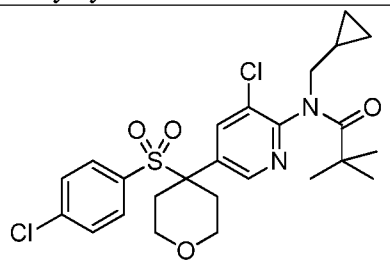
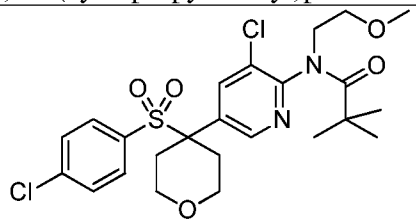
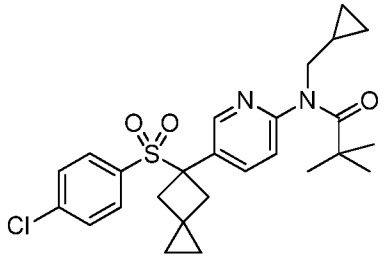


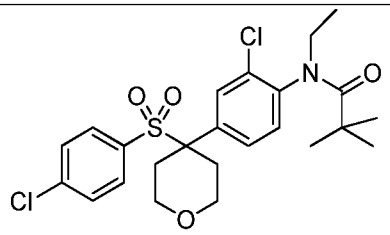
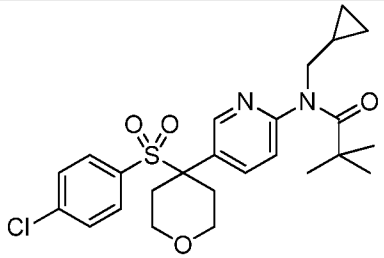
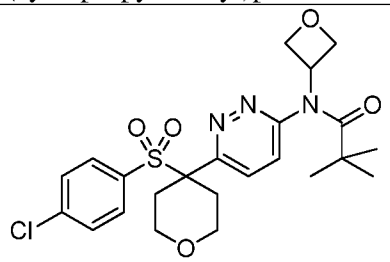
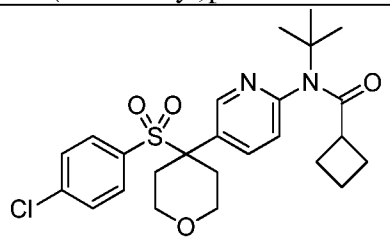
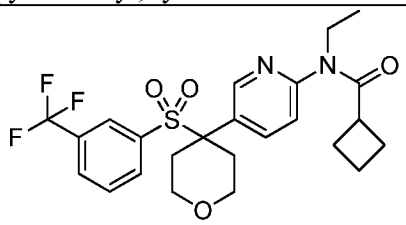
155. The compound of claim 1, wherein the compound of Formula I is:

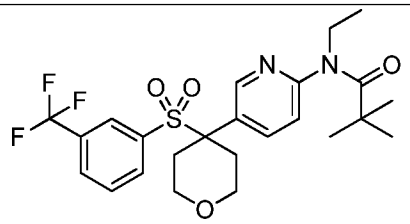
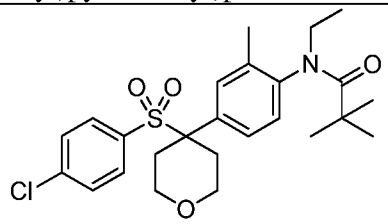
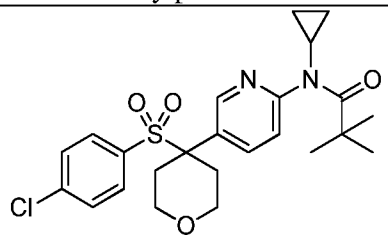
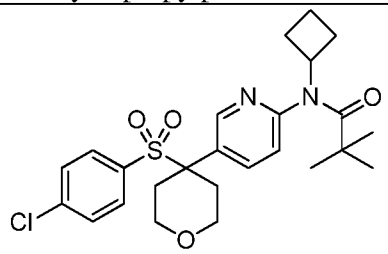
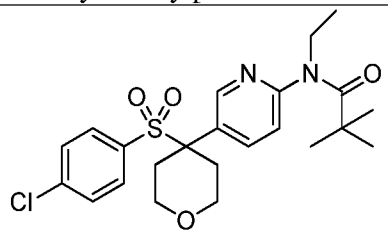
Ex #	Structure
1	 N-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-methylphenyl)-N-isopropylpivalamide
2	 *N*-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyrimidin-2-yl)-*N*-ethylpivalamide

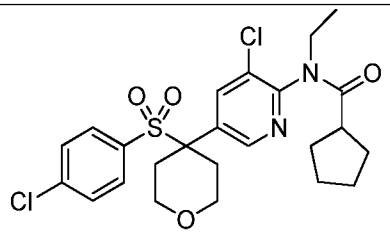
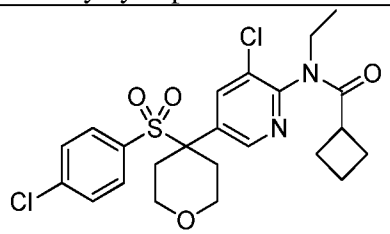
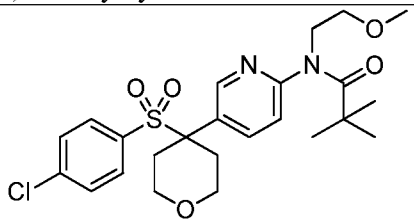
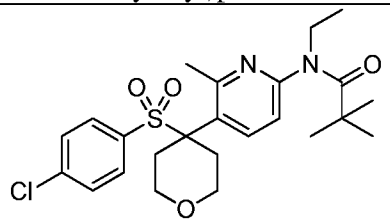
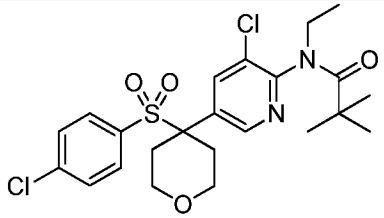
Ex #	Structure
3	 N-(2-chloro-4-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)phenyl)-N-ethylpivalamide
4	 N-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)phenyl)-N-isopropylpivalamide
5	 N-cyclopropyl-N-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)pivalamide
6	 N-(3-chloro-5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-(cyclopropylmethyl)pivalamide
7	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-3-fluoropyridin-2-yl)-N-ethylpivalamide

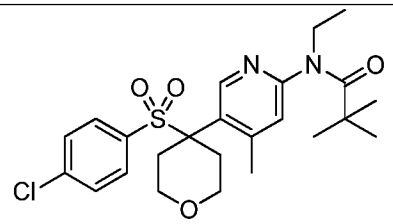
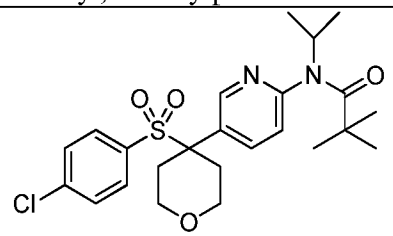
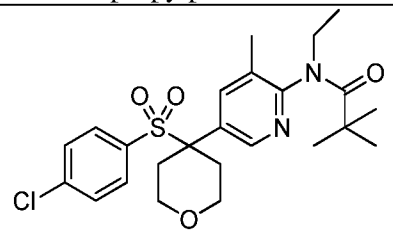
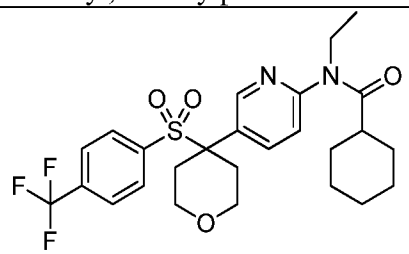
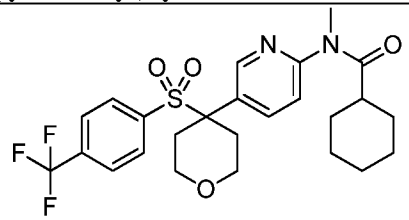
Ex #	Structure
8	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-cyclopropylpivalamide
9	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyrimidin-2-yl)-N-ethylpivalamide
10	 N-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-N-isopropylpivalamide
11	 N-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-N-ethylpivalamide
12	 N-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-N-ethylcyclopentanecarboxamide

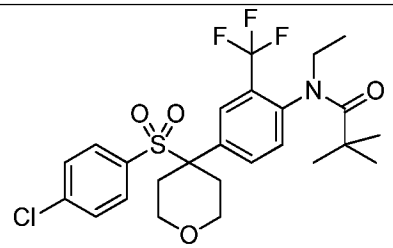
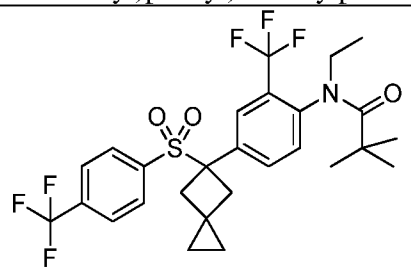
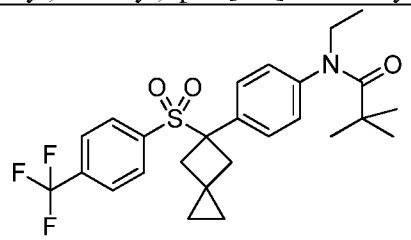
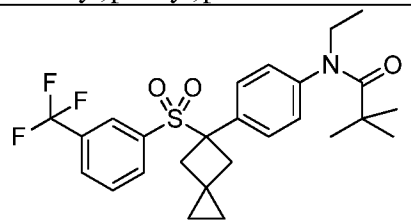
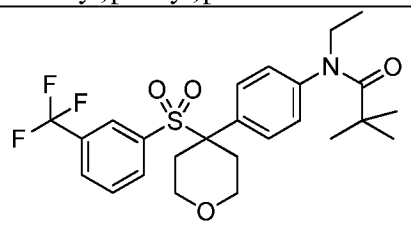
Ex #	Structure
13	 N-(5-(1-((4-chlorophenyl)sulfonyl)cyclopent-3-en-1-yl)pyridin-2-yl)-N-ethylpivalamide
14	 N-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-N-ethylcyclobutanecarboxamide
15	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-(cyclopropylmethyl)pivalamide
16	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-(2-methoxyethyl)pivalamide
17	 N-(5-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)-N-(cyclopropylmethyl)pivalamide

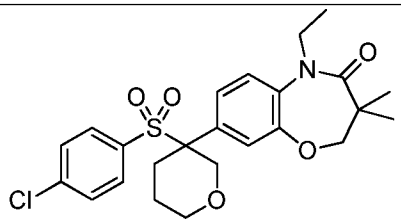
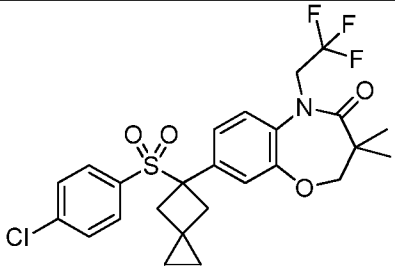
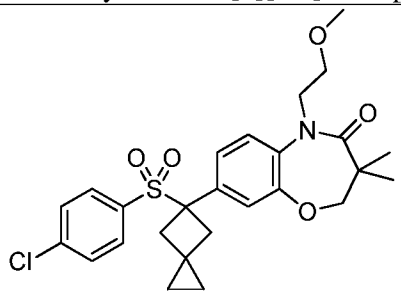
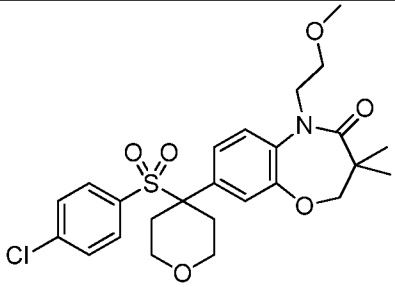
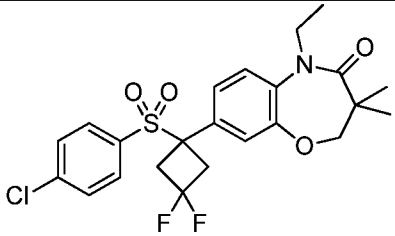
Ex #	Structure
18	 N-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)phenyl)-N-ethylpivalamide
19	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-(cyclopropylmethyl)pivalamide
20	 N-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridazin-3-yl)-N-(oxetan-3-yl)pivalamide
21	 N-(tert-butyl)-N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclobutanecarboxamide
22	 N-ethyl-N-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclobutanecarboxamide

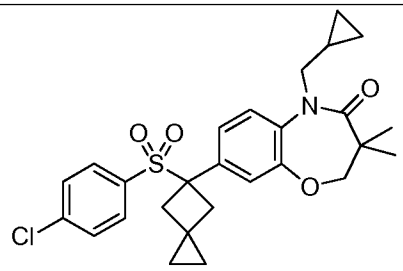
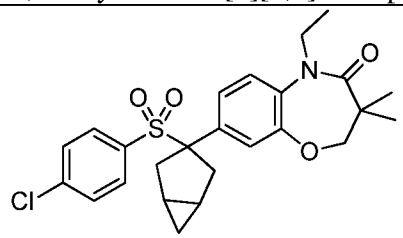
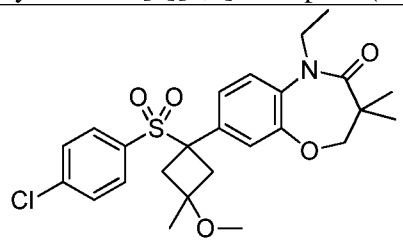
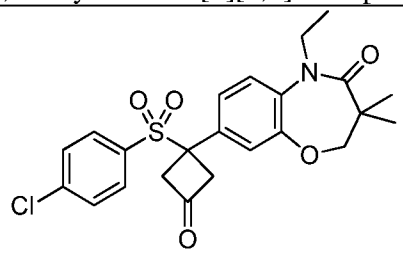
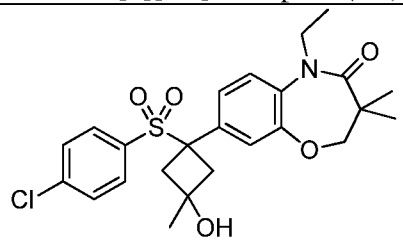
Ex #	Structure
23	 N-ethyl-N-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)pivalamide
24	 N-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-methylphenyl)-N-ethylpivalamide
25	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-cyclopropylpivalamide
26	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-cyclobutylpivalamide
27	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-ethylpivalamide

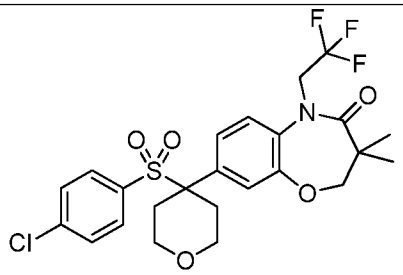
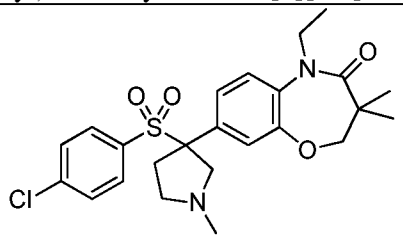
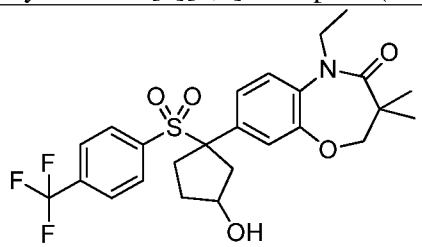
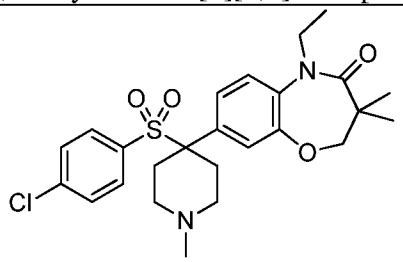
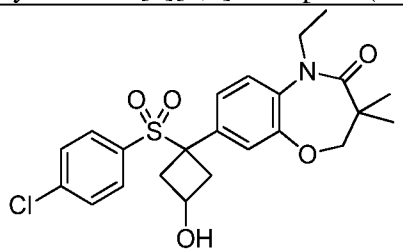
Ex #	Structure
28	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-ethylcyclopentanecarboxamide
29	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-ethylcyclobutanecarboxamide
30	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-(2-methoxyethyl)pivalamide
31	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-6-methylpyridin-2-yl)-N-ethylpivalamide
32	 N-(3-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-ethylpivalamide

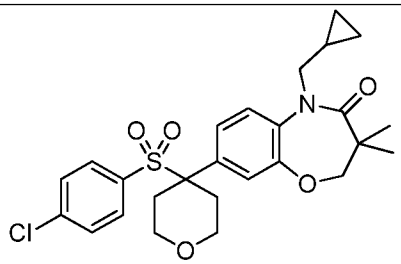
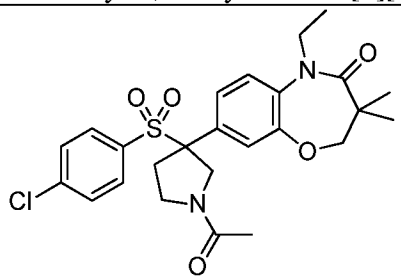
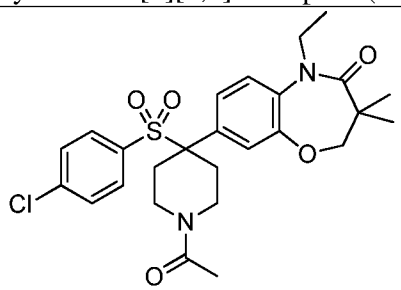
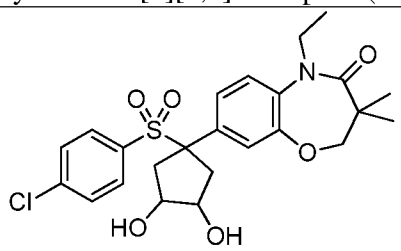
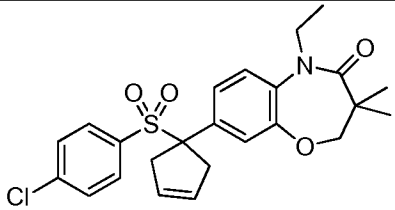
Ex #	Structure
33	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-4-methylpyridin-2-yl)-N-ethylpivalamide
34	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-N-isopropylpivalamide
35	 N-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-3-methylpyridin-2-yl)-N-ethylpivalamide
36	 N-ethyl-N-(5-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclohexanecarboxamide
37	 N-methyl-N-(5-(4-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)pyridin-2-yl)cyclohexanecarboxamide

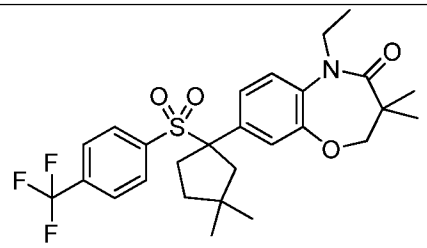
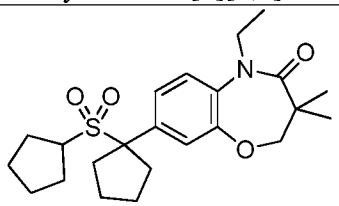
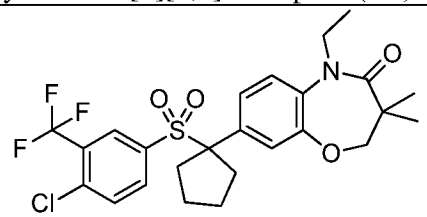
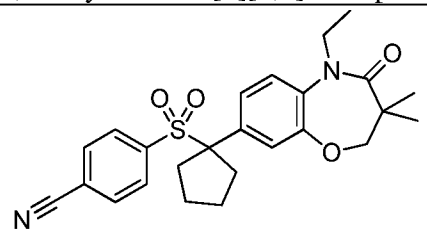
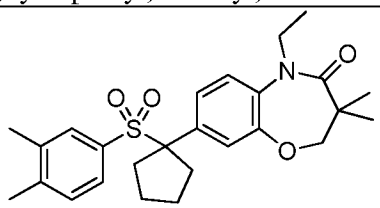
Ex #	Structure
38	 N-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenyl)-N-ethylpivalamide
39	 N-ethyl-N-(2-(trifluoromethyl)-4-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
40	 N-ethyl-N-(4-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
41	 N-ethyl-N-(4-(5-((3-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)pivalamide
42	 N-ethyl-N-(4-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)phenyl)pivalamide

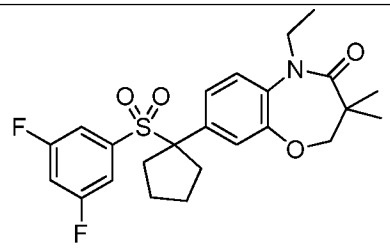
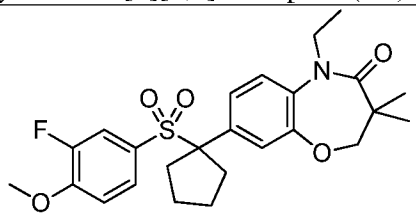
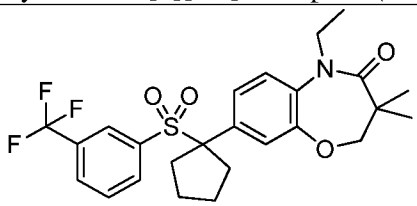
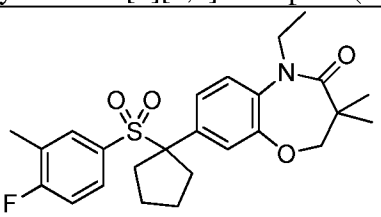
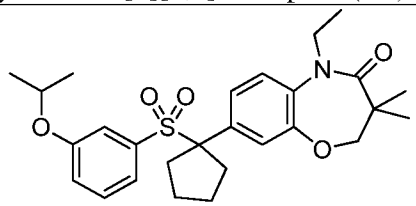
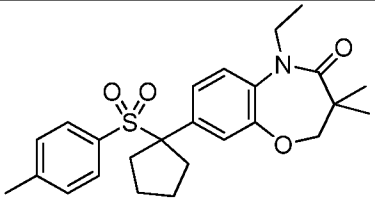
Ex #	Structure
43	 8-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
44	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-3,3-dimethyl-5-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
45	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-5-(2-methoxyethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
46	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-(2-methoxyethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
47	 8-(1-((4-chlorophenyl)sulfonyl)-3,3-difluorocyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

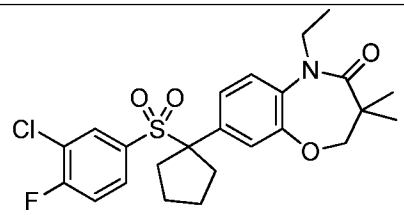
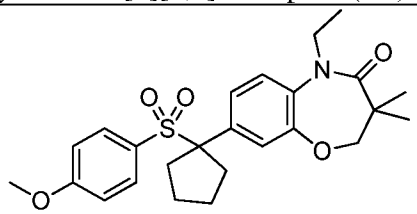
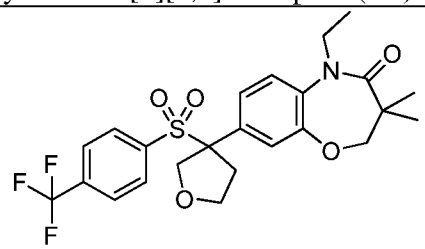
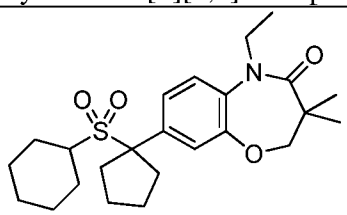
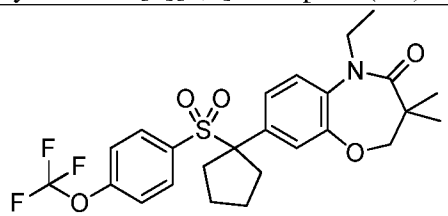
Ex #	Structure
48	 8-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-5-(cyclopropylmethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
49	 8-(3-((4-chlorophenyl)sulfonyl)bicyclo[3.1.0]hexan-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
50	 8-(1-((4-chlorophenyl)sulfonyl)-3-methoxy-3-methylcyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
51	 8-(1-((4-chlorophenyl)sulfonyl)-3-oxocyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
52	 8-(1-((4-chlorophenyl)sulfonyl)-3-hydroxy-3-methylcyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

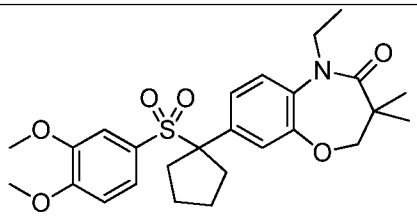
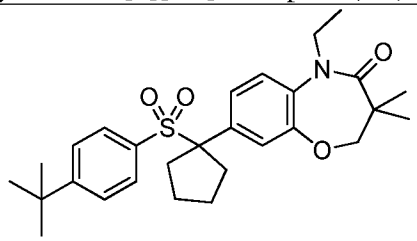
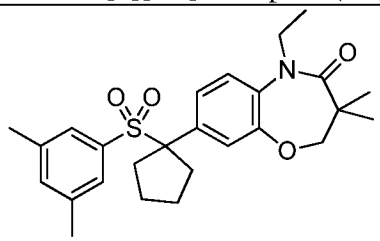
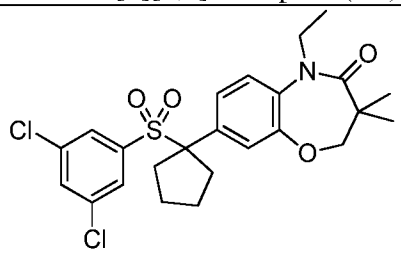
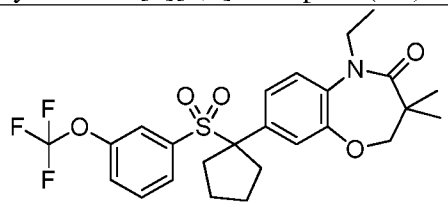
Ex #	Structure
53	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-3,3-dimethyl-5-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
54	 8-(3-((4-chlorophenyl)sulfonyl)-1-methylpyrrolidin-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
55	 5-ethyl-8-(3-hydroxy-1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
56	 8-(4-((4-chlorophenyl)sulfonyl)-1-methylpiperidin-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
57	 8-(1-((4-chlorophenyl)sulfonyl)-3-hydroxycyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

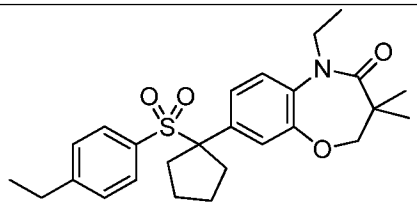
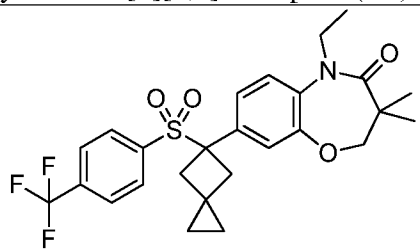
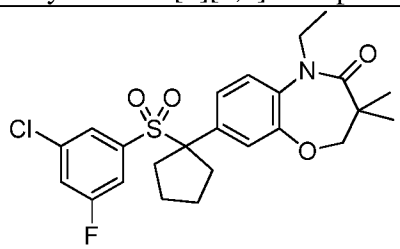
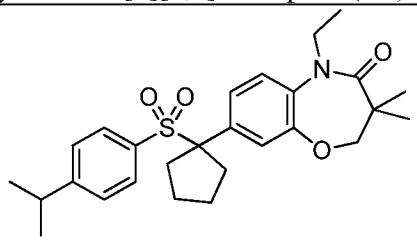
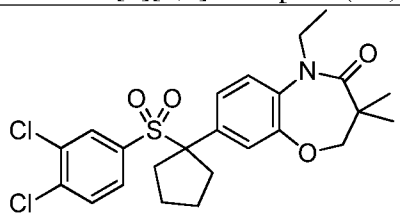
Ex #	Structure
58	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-(cyclopropylmethyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
59	 8-(1-acetyl-3-((4-chlorophenyl)sulfonyl)pyrrolidin-3-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
60	 8-(1-acetyl-4-((4-chlorophenyl)sulfonyl)piperidin-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
61	 8-(1-((4-chlorophenyl)sulfonyl)-3,4-dihydroxycyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
62	 8-(1-((4-chlorophenyl)sulfonyl)cyclopent-3-en-1-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

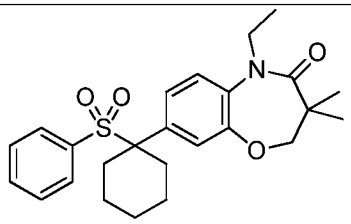
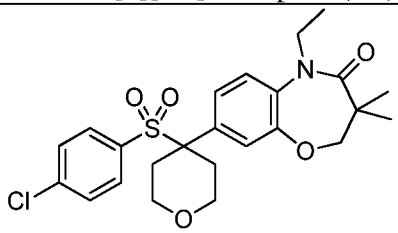
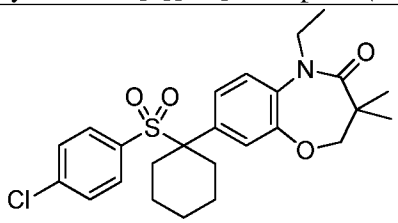
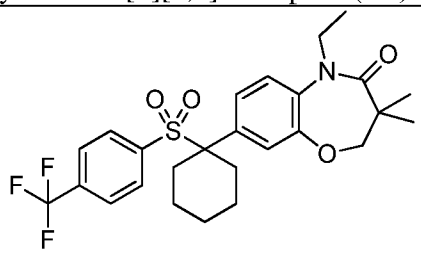
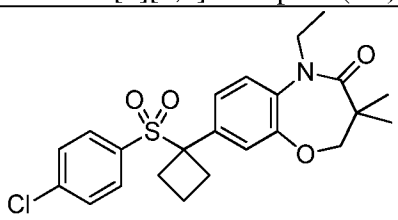
Ex #	Structure
63	 8-(3,3-dimethyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
64	 8-(1-(cyclopentylsulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
65	 8-(1-((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
66	 4-((1-(5-ethyl-3,3-dimethyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-8-yl)cyclopentyl)sulfonyl)benzonitrile
67	 8-(1-((3,4-dimethylphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

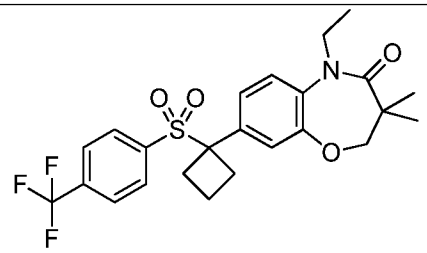
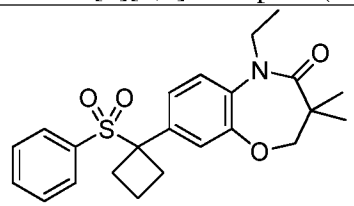
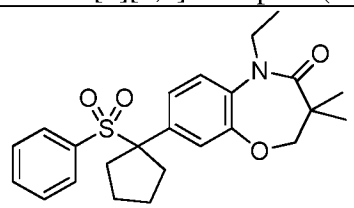
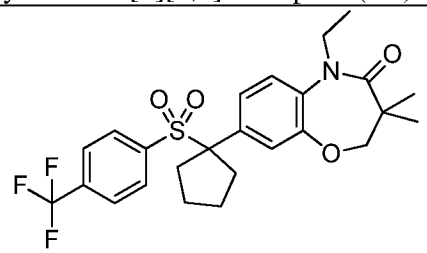
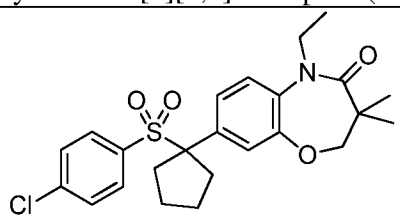
Ex #	Structure
68	 8-(1-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
69	 5-ethyl-8-(1-((3-fluoro-4-methoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
70	 5-ethyl-3,3-dimethyl-8-(1-((3-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
71	 5-ethyl-8-(1-((4-fluoro-3-methylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
72	 5-ethyl-8-(1-((3-isopropoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
73	 5-ethyl-3,3-dimethyl-8-(1-tosylcyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

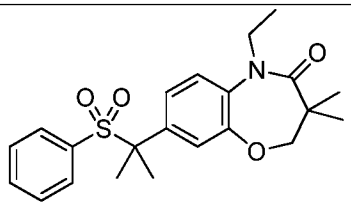
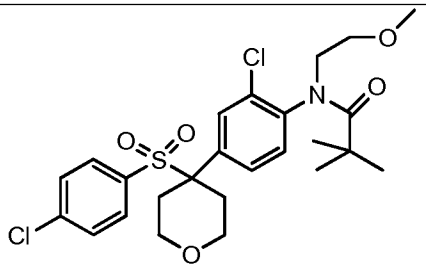
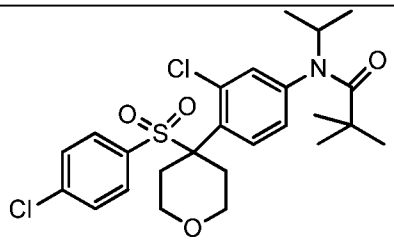
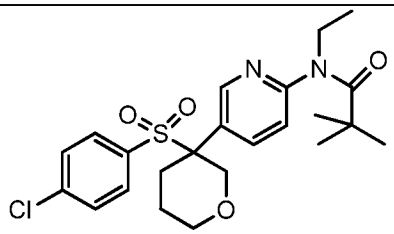
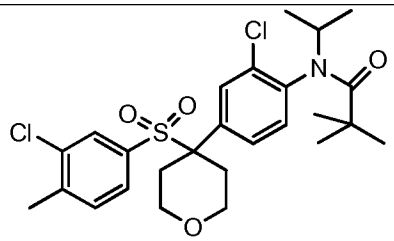
Ex #	Structure
74	 8-(1-((3-chloro-4-fluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
75	 5-ethyl-8-(1-((4-methoxyphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
76	 5-ethyl-3,3-dimethyl-8-(3-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydrofuran-3-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
77	 8-(1-(cyclohexylsulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
78	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

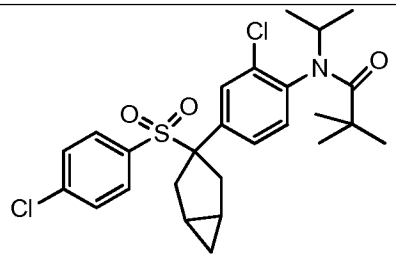
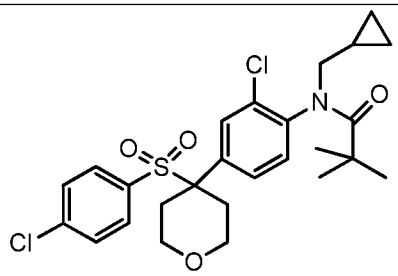
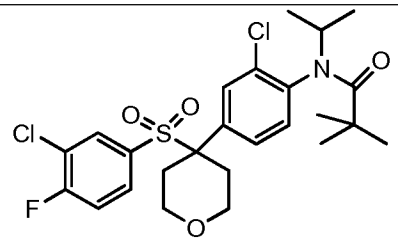
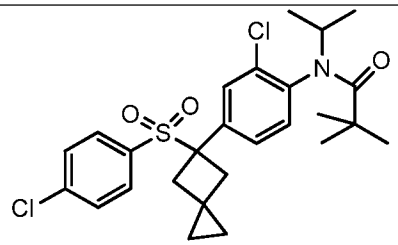
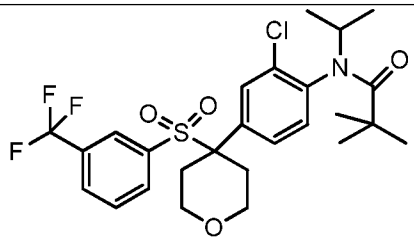
Ex #	Structure
79	 8-(1-((3,4-dimethoxyphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
80	 8-(1-((4-(tert-butyl)phenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
81	 8-(1-((3,5-dimethylphenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
82	 8-(1-((3,5-dichlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
83	 5-ethyl-3,3-dimethyl-8-(1-((3-(trifluoromethoxy)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

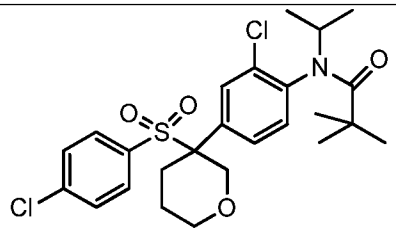
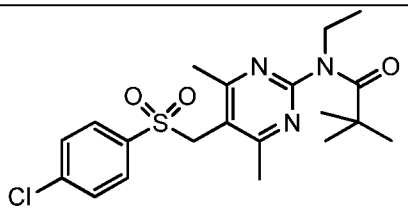
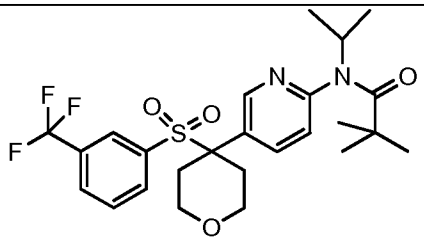
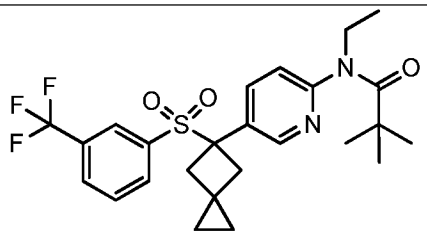
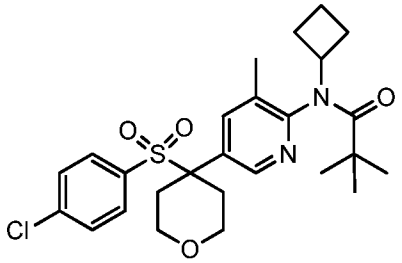
Ex #	Structure
84	 5-ethyl-8-(1-((4-ethylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
85	 5-ethyl-3,3-dimethyl-8-(5-((4-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
86	 8-(1-((3-chloro-5-fluorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
87	 5-ethyl-8-(1-((4-isopropylphenyl)sulfonyl)cyclopentyl)-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
88	 8-(1-((3,4-dichlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

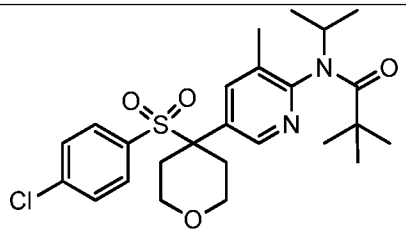
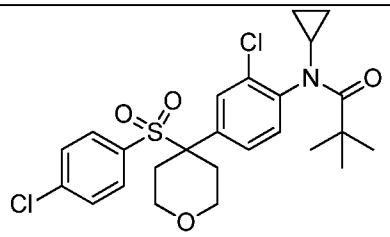
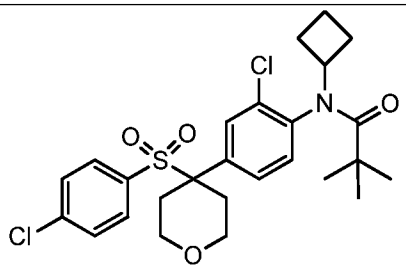
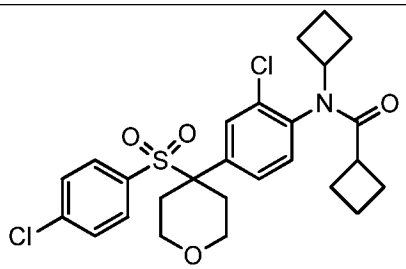
Ex #	Structure
89	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclohexyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
90	 8-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
91	 8-(1-((4-chlorophenyl)sulfonyl)cyclohexyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
92	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclohexyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
93	 8-(1-((4-chlorophenyl)sulfonyl)cyclobutyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

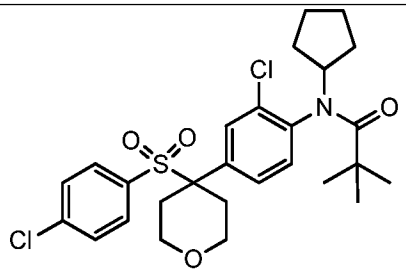
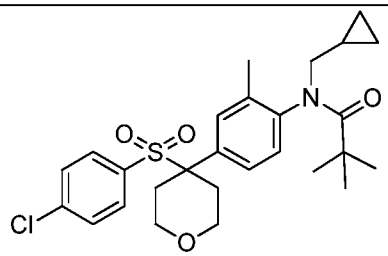
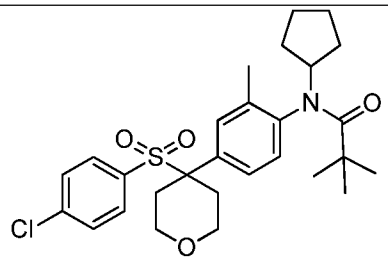
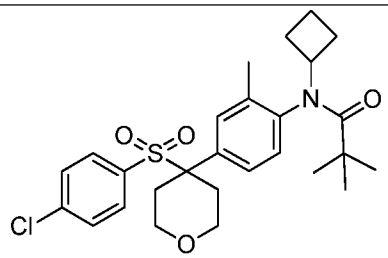
Ex #	Structure
94	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
95	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclobutyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
96	 5-ethyl-3,3-dimethyl-8-(1-(phenylsulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
97	 5-ethyl-3,3-dimethyl-8-(1-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
98	 8-(1-((4-chlorophenyl)sulfonyl)cyclopentyl)-5-ethyl-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

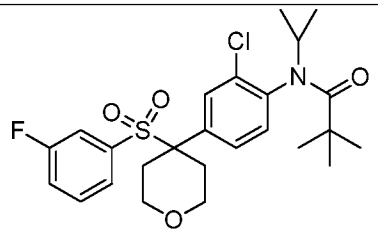
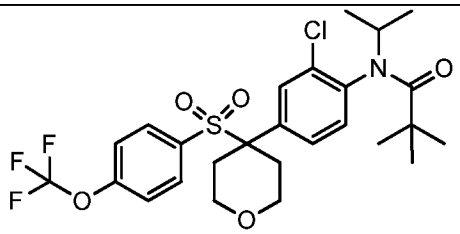
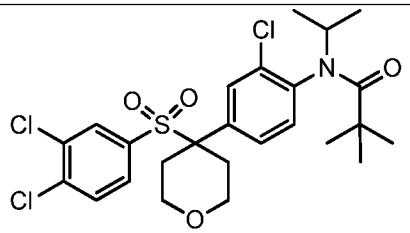
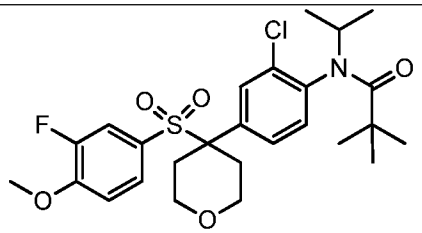
Ex #	Structure
99	 5-ethyl-3,3-dimethyl-8-(2-(phenylsulfonyl)propan-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one
100	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-(2-methoxyethyl)pivalamide
101	 *N*-(3-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
102	 *N*-(5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide
103	 *N*-(2-chloro-4-(4-((3-chloro-4-methylphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

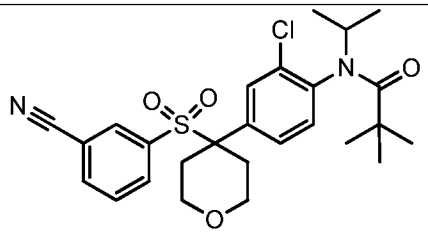
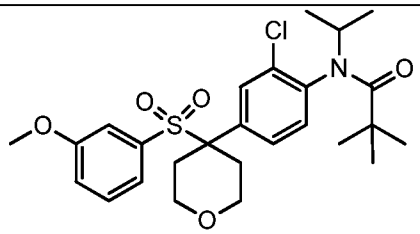
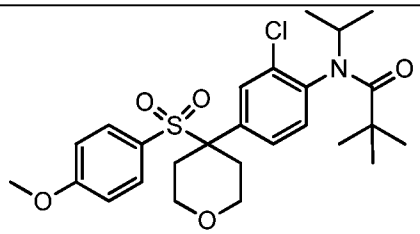
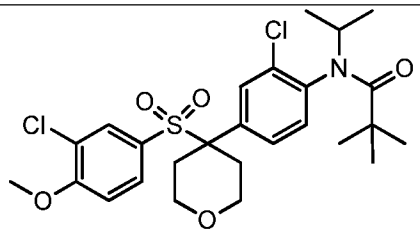
Ex #	Structure
104	 *N*-(2-chloro-4-(3-((4-chlorophenyl)sulfonyl)bicyclo[3.1.0]hexan-3-yl)phenyl)-*N*-isopropylpivalamide
105	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-(cyclopropylmethyl)pivalamide
106	 *N*-(2-chloro-4-(4-((3-chloro-4-fluorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
107	 *N*-(2-chloro-4-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)phenyl)-*N*-isopropylpivalamide
108	 *N*-(2-chloro-4-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

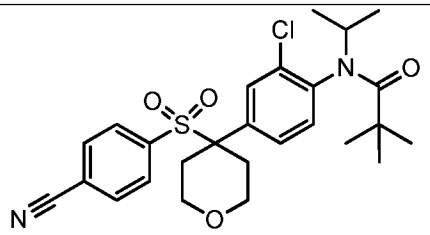
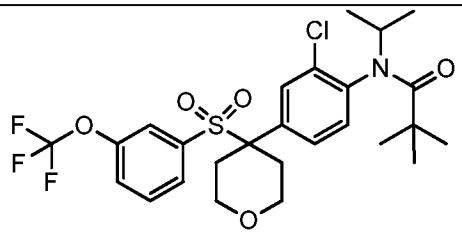
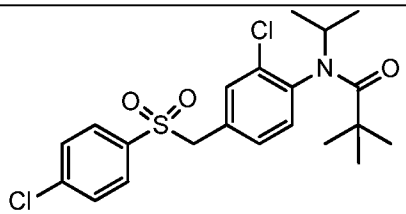
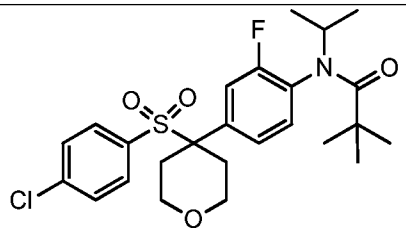
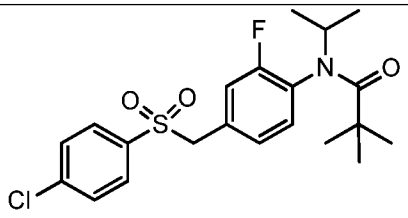
Ex #	Structure
109	 *N*-(2-chloro-4-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)phenyl)-*N*-isopropylpivalamide
110	 *N*-(5-(((4-chlorophenyl)sulfonyl)methyl)-4,6-dimethylpyrimidin-2-yl)-*N*-ethylpivalamide
111	 *N*-isopropyl-*N*-(5-(4-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)pivalamide
112	 *N*-ethyl-*N*-(5-(5-((3-(trifluoromethyl)phenyl)sulfonyl)spiro[2.3]hexan-5-yl)pyridin-2-yl)pivalamide
113	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-cyclobutylpivalamide

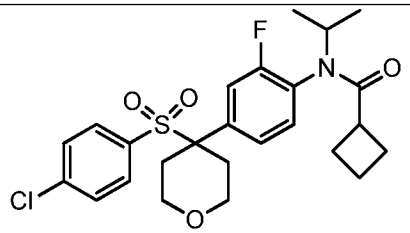
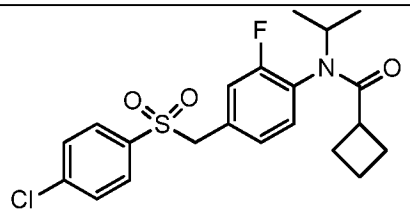
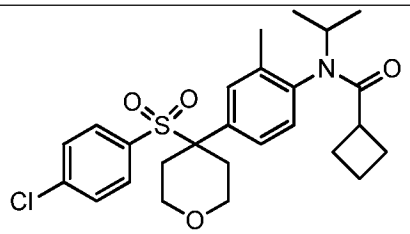
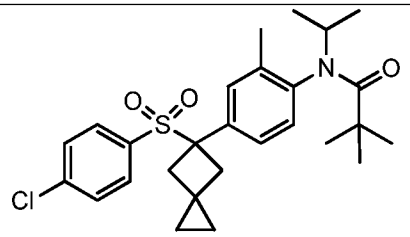
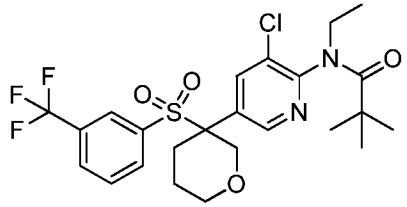
Ex #	Structure
114	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-isopropylpivalamide
115	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclopropylpivalamide
116	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylpivalamide
117	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylcyclobutanecarboxamide

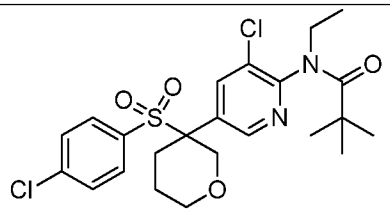
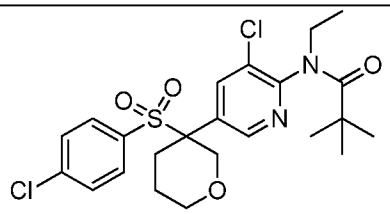
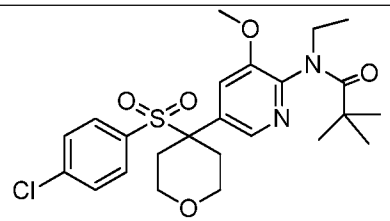
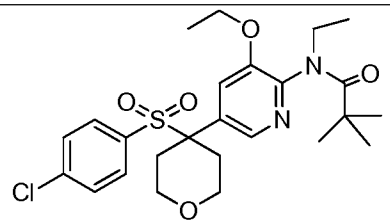
Ex #	Structure
118	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclopentylpivalamide
119	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-(cyclopropylmethyl)pivalamide
120	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-cyclopentylpivalamide
121	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-cyclobutylpivalamide

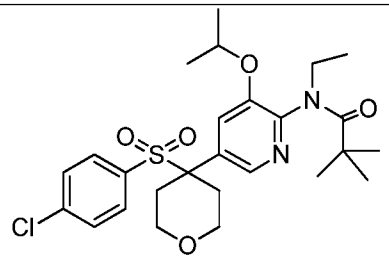
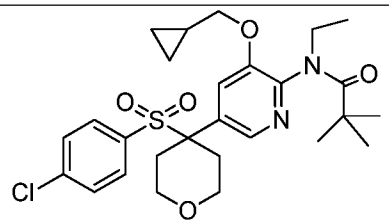
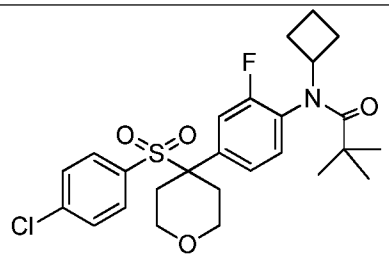
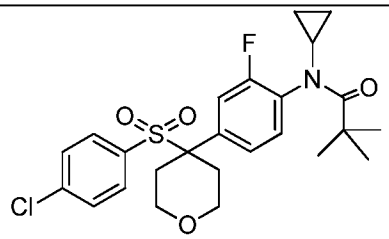
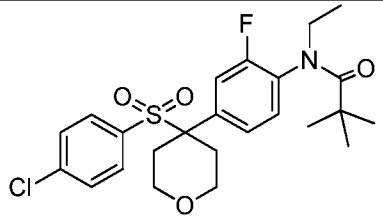
Ex #	Structure
122	 *N*-(2-chloro-4-(4-((3-fluorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
123	 *N*-(2-chloro-4-(4-((4-(trifluoromethoxy)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
124	 *N*-(2-chloro-4-(4-((3,4-dichlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
125	 *N*-(2-chloro-4-(4-((3-fluoro-4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

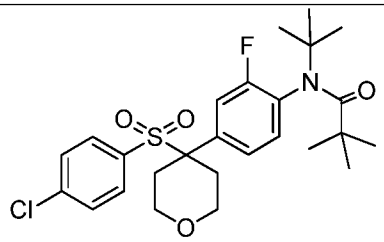
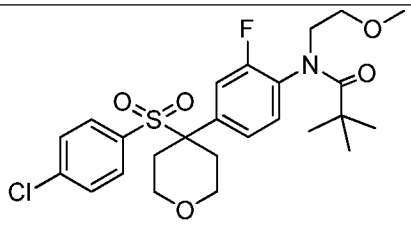
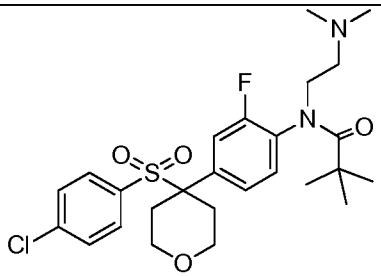
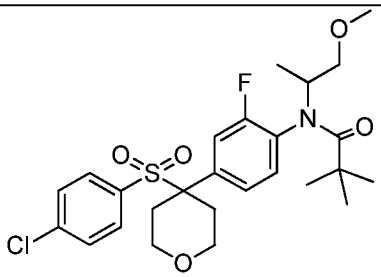
Ex #	Structure
126	 *N*-(2-chloro-4-(4-((3-cyanophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
127	 *N*-(2-chloro-4-(4-((3-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
128	 *N*-(2-chloro-4-(4-((4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
129	 *N*-(2-chloro-4-(4-((3-chloro-4-methoxyphenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide

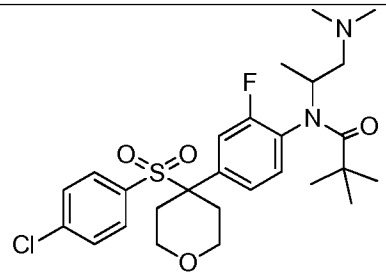
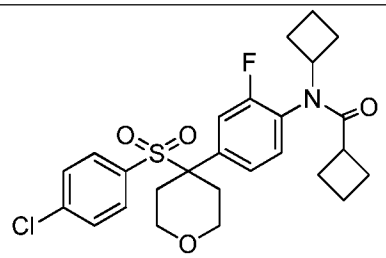
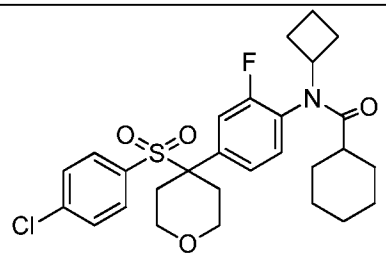
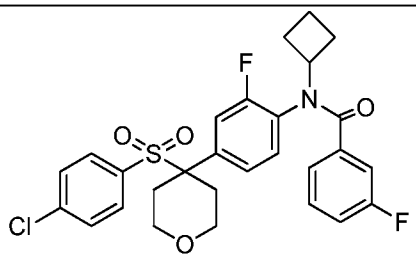
Ex #	Structure
130	 *N*-(2-chloro-4-(4-((4-cyanophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
131	 *N*-(2-chloro-4-(4-((3-(trifluoromethoxy)phenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
132	 *N*-(2-chloro-4-(((4-chlorophenyl)sulfonyl)methyl)phenyl)-*N*-isopropylpivalamide
133	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpivalamide
134	 *N*-(4-(((4-chlorophenyl)sulfonyl)methyl)-2-fluorophenyl)-*N*-isopropylpivalamide

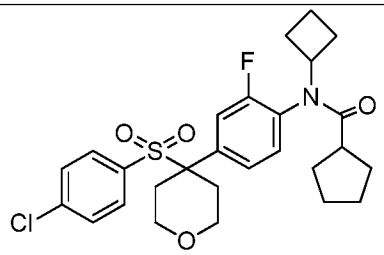
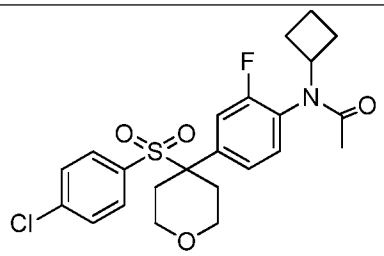
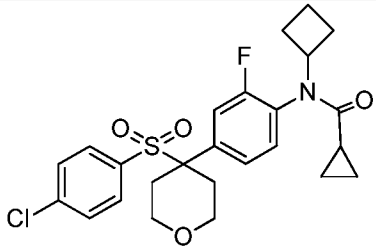
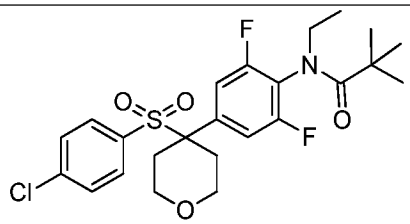
Ex #	Structure
135	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylcyclobutanecarboxamide
136	 *N*-(4-(((4-chlorophenyl)sulfonyl)methyl)-2-fluorophenyl)-*N*-isopropylcyclobutanecarboxamide
137	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylphenyl)-*N*-isopropylcyclobutanecarboxamide
138	 *N*-(4-(5-((4-chlorophenyl)sulfonyl)spiro[2.3]hexan-5-yl)-2-methylphenyl)-*N*-isopropylpivalamide
139	 *N*-(3-chloro-5-(3-((3-(trifluoromethyl)phenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide

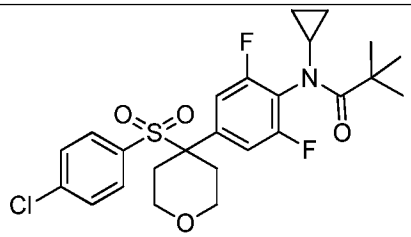
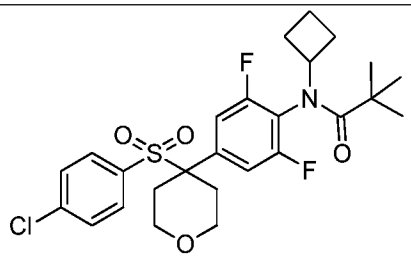
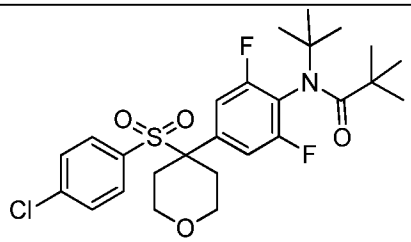
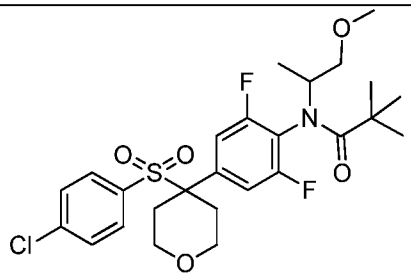
Ex #	Structure
140	 *N*-(3-chloro-5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide enantiomer 1
141	 *N*-(3-chloro-5-(3-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-3-yl)pyridin-2-yl)-*N*-ethylpivalamide enantiomer 2
148	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methoxypyridin-2-yl)-*N*-ethylpivalamide
149	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-ethoxypyridin-2-yl)-*N*-ethylpivalamide

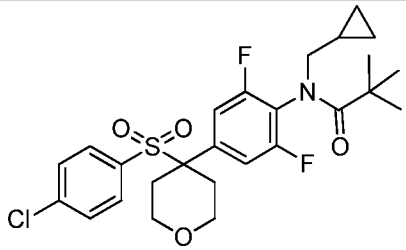
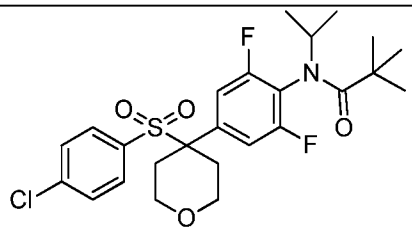
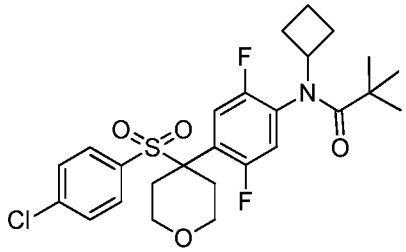
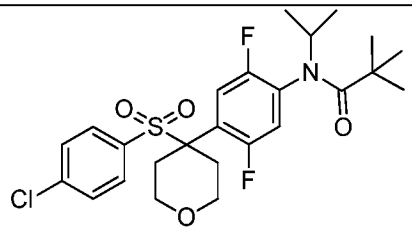
Ex #	Structure
150	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-isopropoxypyridin-2-yl)-*N*-ethylpivalamide
151	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-(cyclopropylmethoxy)pyridin-2-yl)-*N*-ethylpivalamide
152	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylpivalamide
153	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclopropylpivalamide
154	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-ethylpivalamide

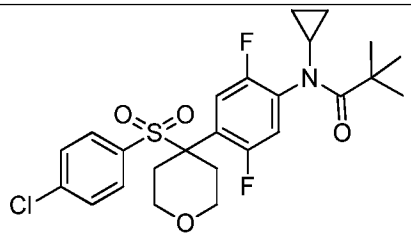
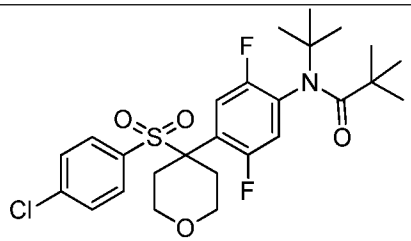
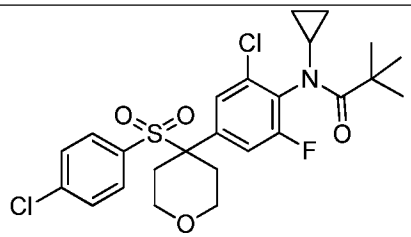
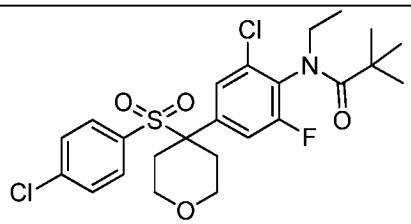
Ex #	Structure
155	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)pivalamide
156	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-methoxyethyl)pivalamide
157	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-(dimethylamino)ethyl)pivalamide
158	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-methoxypropan-2-yl)pivalamide

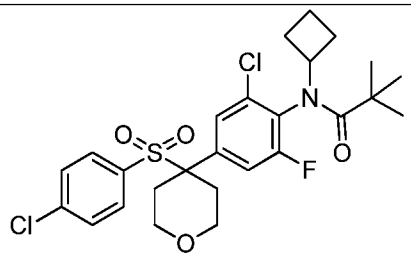
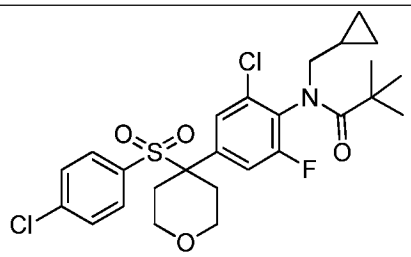
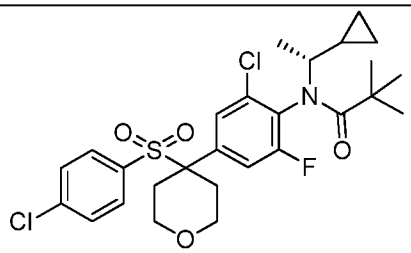
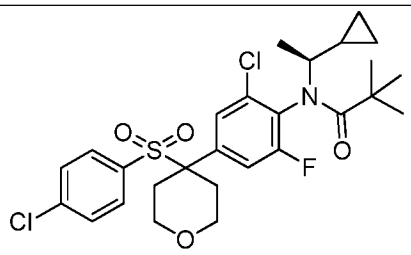
Ex #	Structure
159	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-(dimethylamino)propan-2-yl)pivalamide
160	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclobutanecarboxamide
161	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclohexanecarboxamide
162	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutyl-3-fluorobenzamide

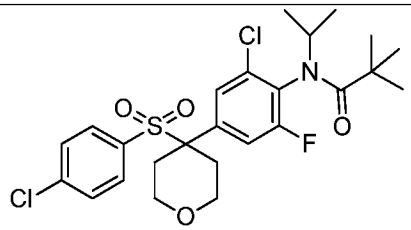
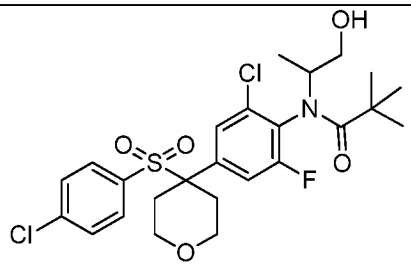
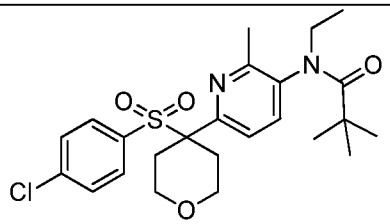
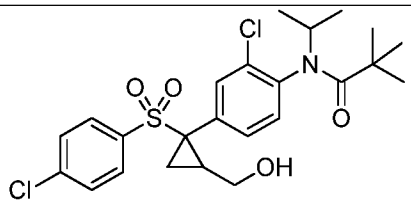
Ex #	Structure
163	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclopentanecarboxamide
164	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylacetamide
165	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylcyclopropanecarboxamide
166	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-ethylpivalamide

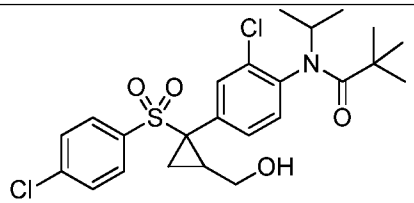
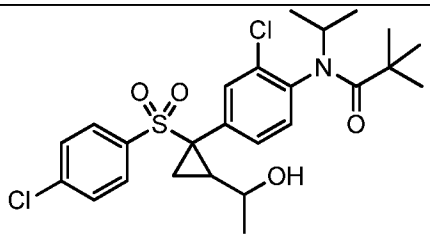
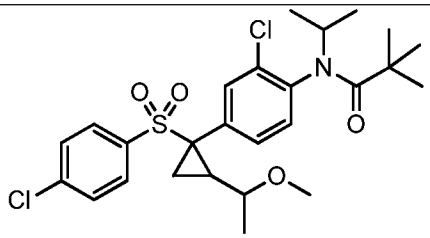
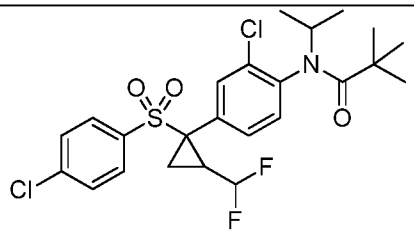
Ex #	Structure
167	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-cyclopropylpivalamide
168	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-cyclobutylpivalamide
169	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)pivalamide
170	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-(1-methoxypropan-2-yl)pivalamide

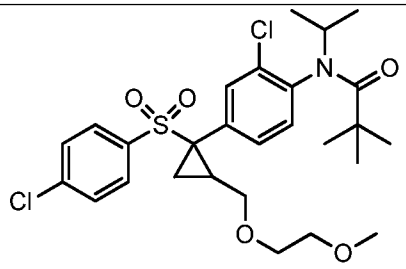
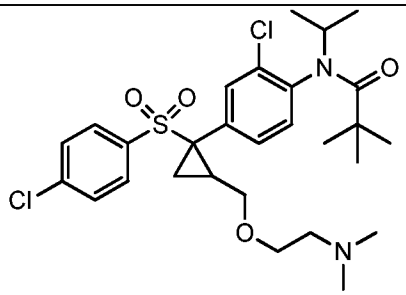
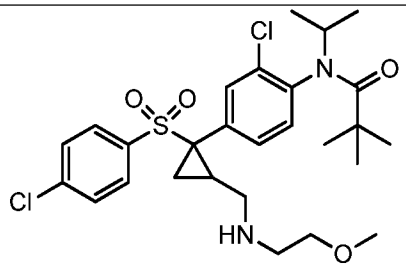
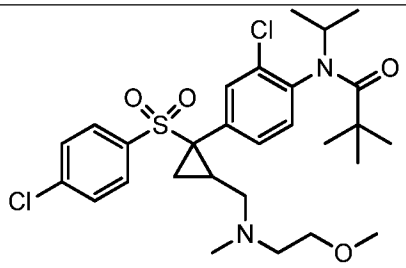
Ex #	Structure
171	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-(cyclopropylmethyl)pivalamide
172	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,6-difluorophenyl)-*N*-isopropylpivalamide
173	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-cyclobutylpivalamide
174	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-isopropylpivalamide

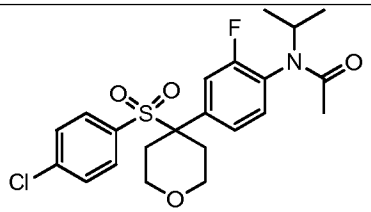
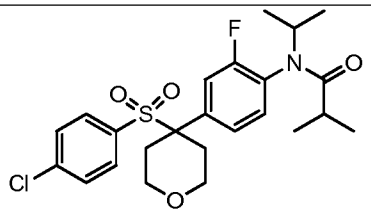
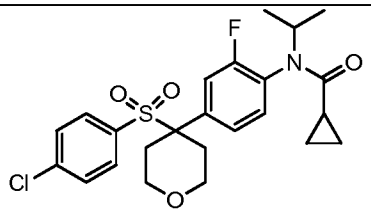
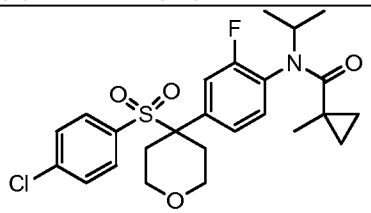
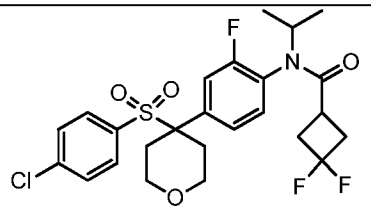
Ex #	Structure
175	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)-*N*-cyclopropylpivalamide
176	 *N*-(*tert*-butyl)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2,5-difluorophenyl)pivalamide
177	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-cyclopropylpivalamide
178	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-ethylpivalamide

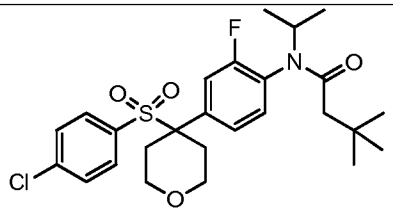
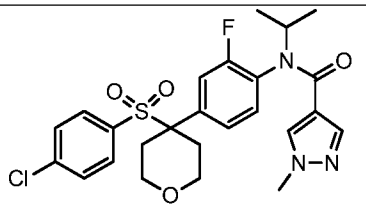
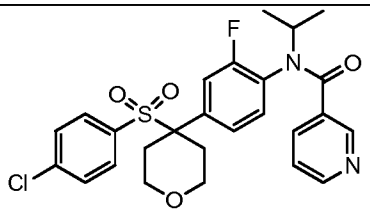
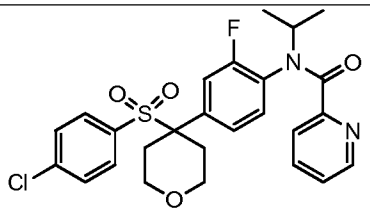
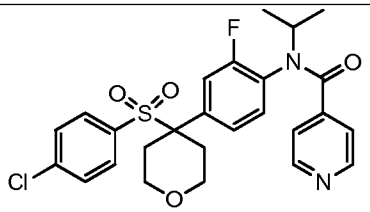
Ex #	Structure
179	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-cyclobutylpivalamide
180	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(cyclopropylmethyl)pivalamide
181	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide
182	 (*S*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide

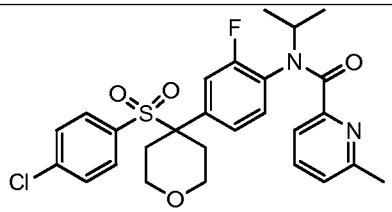
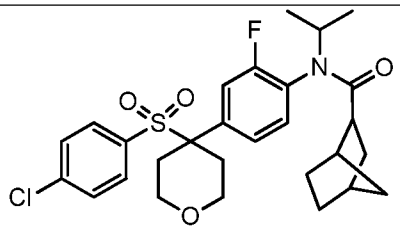
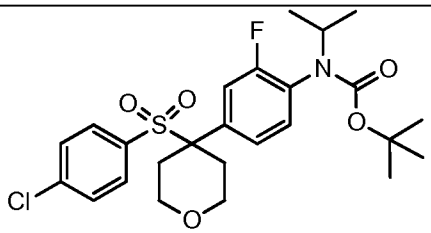
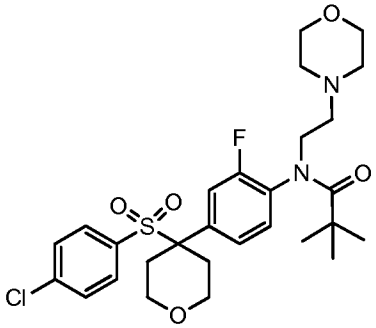
Ex #	Structure
183	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-isopropylpivalamide
184	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-hydroxypropan-2-yl)pivalamide
185	 *N*-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methylpyridin-3-yl)-*N*-ethylpivalamide
187	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(hydroxymethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide isomer 1

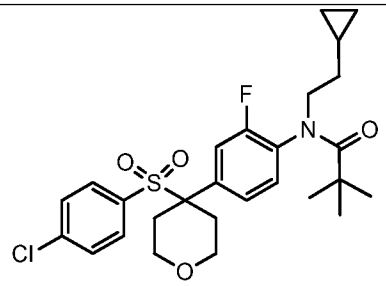
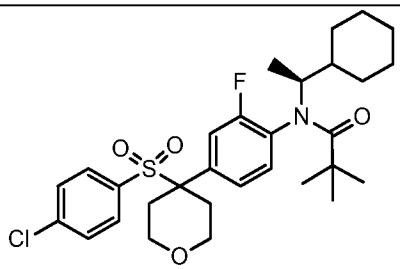
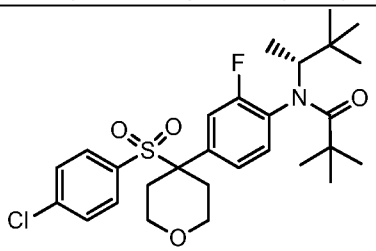
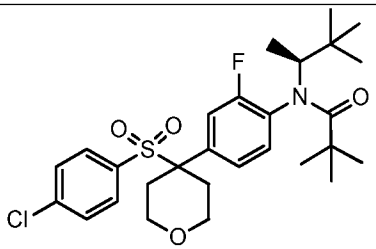
Ex #	Structure
188	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(hydroxymethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide isomer 2
189	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(1-hydroxyethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
190	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(1-methoxyethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
191	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(difluoromethyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide

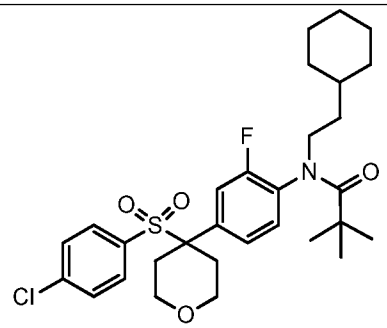
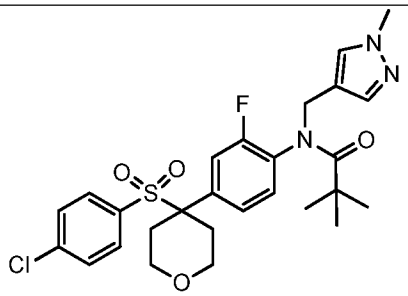
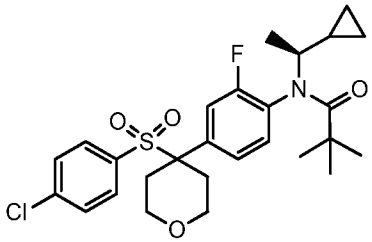
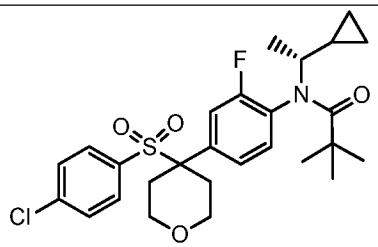
Ex #	Structure
192	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-((2-methoxyethoxy)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
193	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-((2-(dimethylamino)ethoxy)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
194	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(((2-methoxyethyl)amino)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide
195	 *N*-(2-chloro-4-(1-((4-chlorophenyl)sulfonyl)-2-(((2-methoxyethyl)(methyl)amino)methyl)cyclopropyl)phenyl)-*N*-isopropylpivalamide

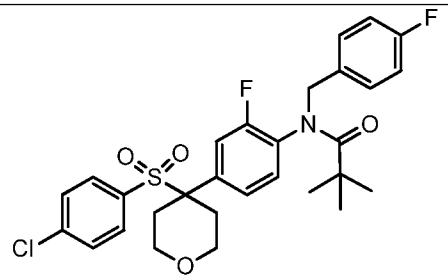
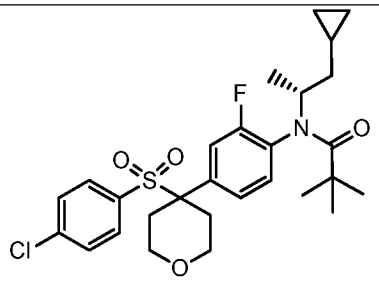
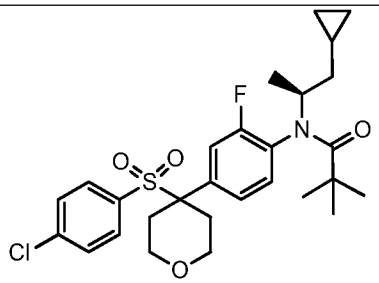
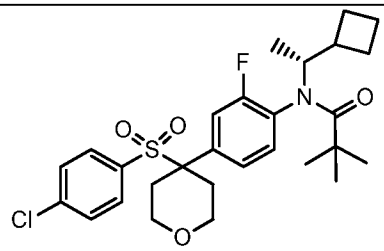
Ex #	Structure
196	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylacetamide
197	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylisobutyramide
198	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylcyclopropanecarboxamide
199	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-1-methylcyclopropanecarboxamide
200	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-3,3-difluoro-*N*-isopropylcyclobutanecarboxamide

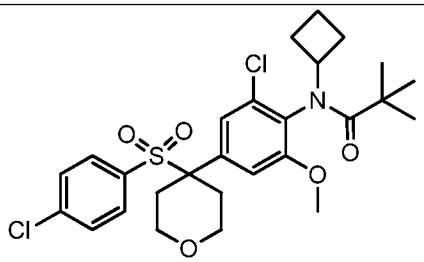
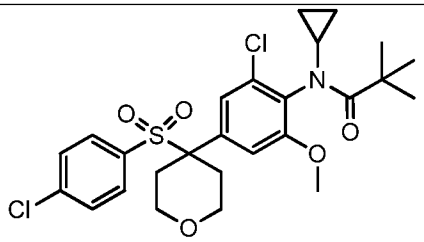
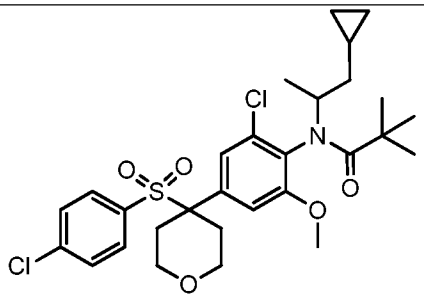
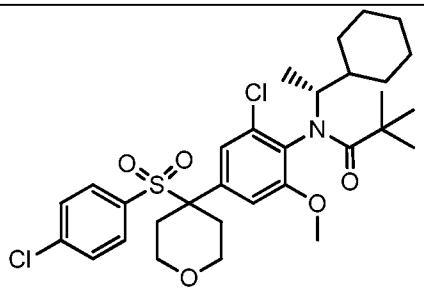
Ex #	Structure
201	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-3,3-dimethylbutanamide
202	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-1-methyl-1*H*-pyrazole-4-carboxamide
203	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylnicotinamide
204	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpicolinamide
205	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylisonicotinamide

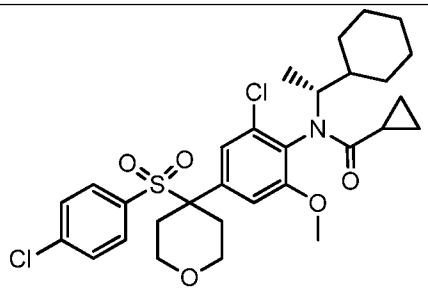
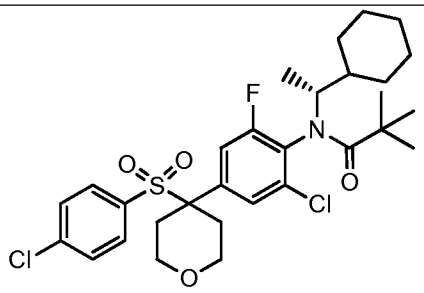
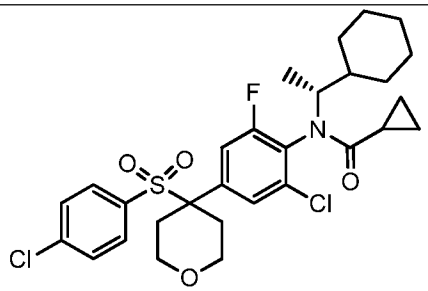
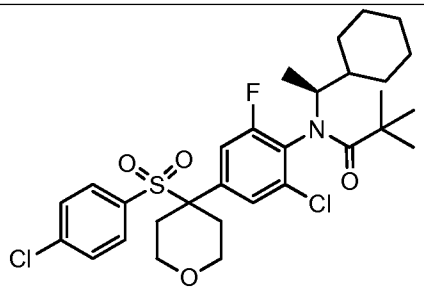
Ex #	Structure
206	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropyl-6-methylpicolinamide
207	 (1*R*,4*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylbicyclo[2.2.1]heptane-2-carboxamide
208	 *tert*-butyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate
209	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-morpholinoethyl)pivalamide

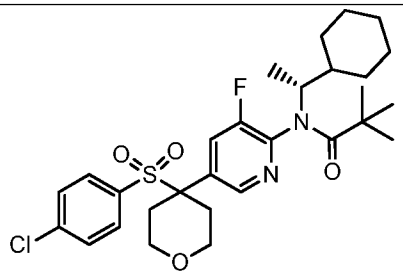
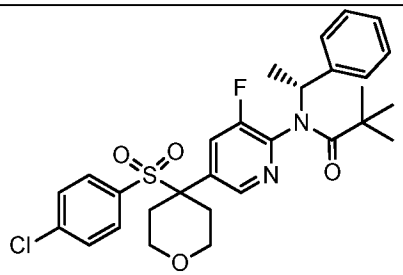
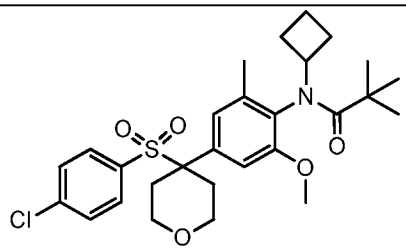
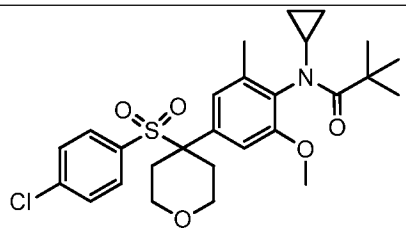
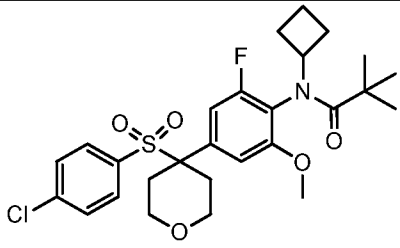
Ex #	Structure
210	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-cyclopropylethyl)pivalamide
211	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide
212	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(3,3-dimethylbutan-2-yl)pivalamide
213	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(3,3-dimethylbutan-2-yl)pivalamide

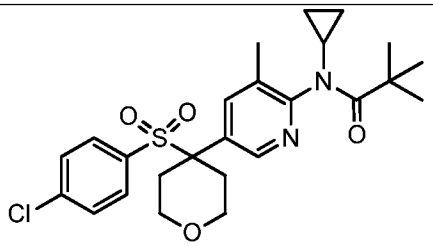
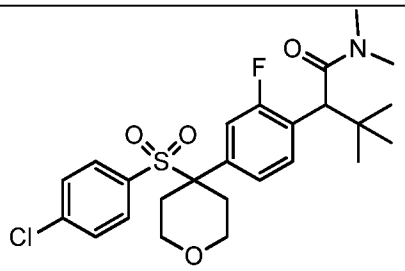
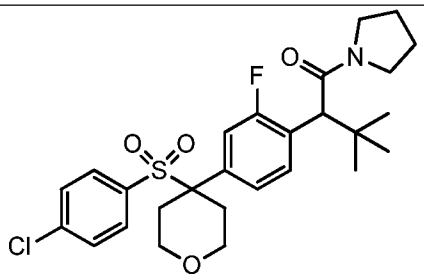
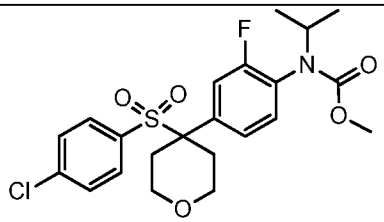
Ex #	Structure
214	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(2-cyclohexylethyl)pivalamide
215	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl)pivalamide
216	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide
217	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylethyl)pivalamide

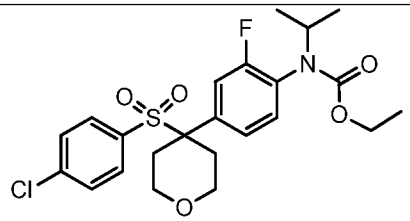
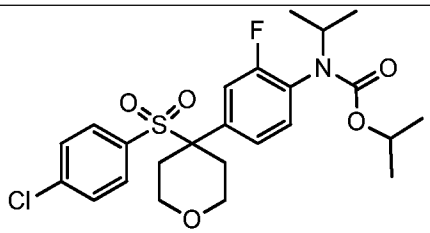
Ex #	Structure
218	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(4-fluorobenzyl)pivalamide
219	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
220	 (*S*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
221	 (*R*)-*N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-(1-cyclobutylethyl)pivalamide

Ex #	Structure
222	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-cyclobutylpivalamide
223	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-cyclopropylpivalamide
224	 *N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclopropylpropan-2-yl)pivalamide
225	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclohexylethyl)pivalamide

Ex #	Structure
226	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-methoxyphenyl)-*N*-(1-cyclohexylethyl)cyclopropanecarboxamide
227	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide
228	 (*R*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)cyclopropanecarboxamide
229	 (*S*)-*N*-(2-chloro-4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-6-fluorophenyl)-*N*-(1-cyclohexylethyl)pivalamide

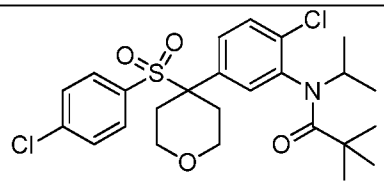
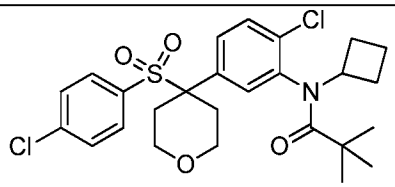
Ex #	Structure
230	 (*R*)-*N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-(1-cyclohexylethyl)pivalamide
231	 (*R*)-*N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-(1-phenylethyl)pivalamide
232	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methoxy-6-methylphenyl)-*N*-cyclobutylpivalamide
233	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-methoxy-6-methylphenyl)-*N*-cyclopropylpivalamide
234	 *N*-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluoro-6-methoxyphenyl)-*N*-cyclobutylpivalamide

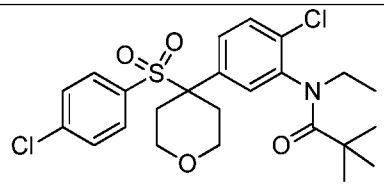
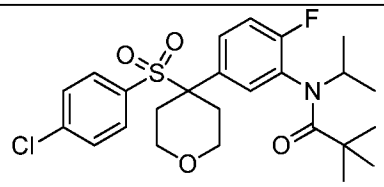
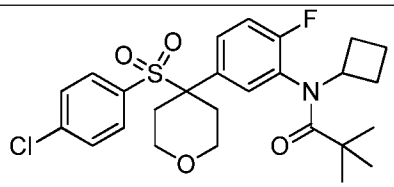
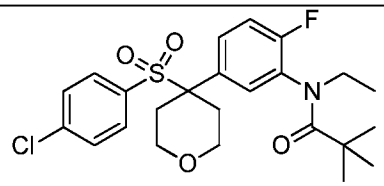
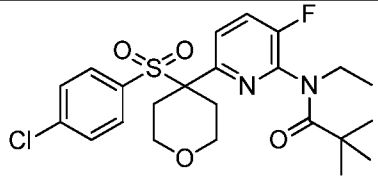
Ex #	Structure
235	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-methylpyridin-2-yl)-*N*-cyclopropylpivalamide
236	 2-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*,*N*,3,3-tetramethylbutanamide
237	 2-(4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one
238	 methyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

Ex #	Structure
239	 ethyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate
240	 isopropyl (4-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)(isopropyl)carbamate

or a pharmaceutically acceptable salt thereof.

156. The compound of claim 5, wherein the compound of Formula Ib is:

Ex #	Structure
142	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-isopropylpivalamide
143	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-cyclobutylpivalamide

Ex #	Structure
144	 *N*-(2-chloro-5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)phenyl)-*N*-ethylpivalamide
145	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2H-pyran-4-yl)-2-fluorophenyl)-*N*-isopropylpivalamide
146	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-cyclobutylpivalamide
147	 *N*-(5-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-2-fluorophenyl)-*N*-ethylpivalamide
186	 *N*-(6-(4-((4-chlorophenyl)sulfonyl)tetrahydro-2*H*-pyran-4-yl)-3-fluoropyridin-2-yl)-*N*-ethylpivalamide

or a pharmaceutically acceptable salt thereof.

157. A pharmaceutical composition comprising the compound of any one of claims 1-156 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or adjuvant.

158. A method of modulating the activity of an ROR-gamma receptor *in vitro* comprising contacting the receptor with the compound of any one of claims 1-156 or a pharmaceutically acceptable salt thereof.

159. A method of modulating the activity of an ROR-gamma receptor *in vivo* comprising contacting the receptor with the compound of any one of claims 1-156 or a pharmaceutically acceptable salt thereof.

160. The method of claim 158 or 159, wherein the compound of any one of claims 1-156 or a pharmaceutically acceptable salt thereof is a modulator of the ROR-gamma receptor.

161. A method of treating or reducing the severity of an ROR-gamma receptor mediated disease in a patient comprising administering the compound of any one of claims 1-156 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

162. The method of claim 161, wherein the disease is selected from the group consisting of Ankylosing, spondylitis, Asthma, Behcet's disease, Chronic obstructive pulmonary disease, Crohn's disease, Diabetes Mellitus Type 1, Multiple Sclerosis, Neuromyelitis optica, Polymyalgia Rheumatica, Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, Scleroderma, Sjögren's syndrome, Systemic Lupus Erythematosus, Systemic sclerosis, Transplant rejection, Inflammatory Bowel Disease, Ulcerative Colitis and Uveitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/055017

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/10 A61P3/10 C07D213/75 C07D309/08 C07D405/04
C07D405/10 C07C317/28 C07C317/30 C07D407/04 C07D239/47
C07D413/04 C07D273/01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/037887 A1 (ASTRAZENECA AB [SE]; ANGST CHRISTOF [US]; HAEBERLEIN MARKUS [SE]; HILL) 8 May 2003 (2003-05-08) example 143 -----	1,15,90, 91, 106-108, 110, 123-127
X	WO 01/64632 A1 (AVENTIS PHARMA SA [FR]) 7 September 2001 (2001-09-07) page 94, lines 9-10 -----	1,2,5, 57,59, 60, 74-77, 90,91, 106-108, 110,111, 123-127, 129-131, 140-143

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2013	28/10/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tabanella, Stefania

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/055017

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/161446 A1 (UNIV NOTTINGHAM [GB]; WANG SHUDONG [GB]; CHAHROUR OSAMA [GB]; LU TIANG) 29 December 2011 (2011-12-29) page 46, line 1 - line 15 -----	1,5,15, 46,63, 64, 74-77, 90,91, 106-108, 112, 123-127, 129-131, 144
A	WO 2011/115892 A1 (GRIFFIN PATRICK R [US]; ROUSH WILLIAM R [US]; KUMAR NARESH [US]; NUHAN) 22 September 2011 (2011-09-22) the whole document -----	1-162

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/055017

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		SI 1263720 T1	31-12-2009
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		CN 103068802 A	24-04-2013
		EP 2582675 A1	24-04-2013
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WO 2011115892 A1	22-09-2011	NONE	